Maternal Illness at the Limits of Fetal Viability

van Eerden, L.

2018

document version
Publisher's PDF, also known as Version of record

Maternal Illness at the Limits of Fetal Viability

Leonoor van Eerden

Voor mijn lieve en sterke zussen

ISBN: 978-94-6361-174-9
Layout and printed by: Optima Grafische Communicatie, Rotterdam, The Netherlands
Cover illustration: Astrid de Waardt

Vrije Universiteit

Maternal Illness at the Limits of Fetal Viability

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor
aan de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. V. Subramaniam,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de Faculteit der Geneeskunde
op maandag 10 december 2018 om 11.45 uur
in de aula van de universiteit,
De Boelelaan 1105

door
Leonoor van Eerden
geboren te Groningen

promotor:	prof.dr. C.J.M. de Groot
copromotoren:	dr. A.C. Bolte
	dr. G.G. Zeeman

Contents

Chapter 1

General introduction

Although most pregnancies are uncomplicated in Western countries, rarely maternal health is compromised by pregnancy specific disorders, such as severe preeclampsia, by concomitant disorders such as malignancies or by worsening of pre-existing conditions, such as cardiac disease or hypertension. Even more rarely, complications during pregnancy occur at an extremely early gestational age, where it is uncertain if the fetus is viable, the so called grey zone of viability[1]. In the developed countries this grey zone of viability ranges from 22 to 25 weeks' gestation, depending on additional unfavorable factors, including severe fetal growth restriction or fetal inflammatory response syndrome. Following the diagnosis of a life-threatening maternal disorder at an extremely early gestational age, counseling women and their significant others should take place on several management options. The first decision to be made is whether terminating the pregnancy improves maternal chances of survival and/or reduction of morbidity. Second, a decision on fetal management should be made. Options to be discussed are termination of pregnancy that is without fetal monitoring, when fetal viability is estimated to be very limited or interventions for fetal indications and without active neonatal care. Generally, this will result in a stillborn baby. Another option is delivery, often by means of caesarean section, with the intention of active neonatal management. This results in the birth of an extreme preterm neonate with concomitant high morbidity and mortality rates[2]. These considerations and decision-making (figure 1), depending on gestational age and additional factors related to viability, have been subject to change over the past decades due to advances in neonatal care.

In these cases of severe maternal illness, at the limits of fetal viability, the following aspects play a role.

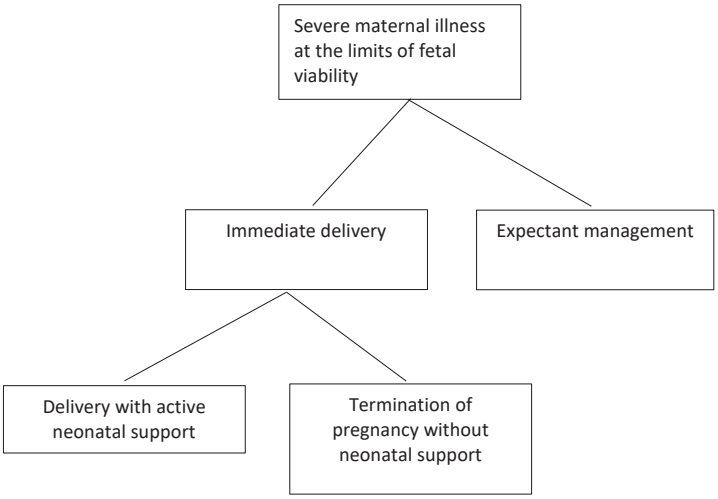


Figure 1. Considerations and decision making in cases of severe maternal illness at the limits of fetal viability

MATERNAL ASPECTS

Maternal health can be compromised by a number of medical conditions.

First, preeclampsia, a pregnancy specific multi-systemic disorder clinically characterized by new onset or worsening of hypertension and presence of either proteinuria or other end organ dysfunction or both after 20 weeks' gestation[3]. It is accountable for a large proportion of maternal and neonatal morbidity and mortality worldwide. For example, preeclampsia is accountable for 14% of maternal deaths worldwide[4]. The etiology is not fully understood yet, but both maternal and placental factors play a role in the development of the disease. Approximately 5% of all pregnancies worldwide are complicated by preeclampsia[5]. Onset before 24 weeks' gestation, however, is very rare with a high maternal morbidity rate up to 65% and a neonatal mortality rate up to 82%[6-7]. At present, the only curative option for preeclampsia is delivery of the fetus and placenta. However, at extreme early gestational ages this will lead to the aforementioned conflict of interests of the mother versus the fetus. Expedited delivery might be in the best interest of the mothers health, however this leads to extreme prematurity with a high risk of neonatal morbidity or mortality[2]. In addition, in pregnancies complicated by preeclampsia, fetuses are often severely growth restricted, further limiting their chances of survival[8]. Besides preeclampsia, there are other pregnancy related conditions that could warrant pregnancy termination. For example: septic or hypovolemic shock with disseminated intravascular coagulation complicating intrauterine infection, uterine rupture, placenta previa with or without abnormal adhesive placentation or placental abruption.

Pre-existing conditions can worsen during pregnancy. In many countries maternal heart disease (acquired or congenital) is the major cause of indirect maternal mortality. Due to the advances in the treatment of these women in the past 50 years, more women are surviving and reach the child-bearing age[9]. Since pregnancy is associated with a 50% increase in plasma volume load, as well as many other pregnancy-related hemodynamic adaptations, in some instances a life-threatening deterioration in maternal cardiac hemodynamics may occur. Women with pre-existing cardiac conditions should be counseled based on the WHO classification. Women with a WHO classification III (at high risk, for instance women with mechanical valves) will need intensive specialist cardiac and obstetric monitoring throughout pregnancy, childbirth and the puerperium. Women with a WHO classification IV (for instance women with severe valve stenosis or significant pulmonary hypertension) are counseled against pregnancy. However, if pregnancy does occur, these women should be counseled on the likelihood that their condition could deteriorate during pregnancy and that in this case termination of pregnancy will be discussed[10-11].

Other pre-existing conditions that are known for potential worsening during pregnancy are, but not limited to: systemic lupus erytematosus and other auto-immune dis-

orders and (end stage) chronic kidney disease[12-13]. When worsening during pregnancy these conditions can lead to irreversible maternal damage and maternal death.

FETAL ASPECTS

The limit of viability is defined as the stage of fetal maturity that ensures a reasonable chance of survival outside the womb. With active intervention, infants born at 25 weeks and above have a high likelihood of survival, whilst infants born below 22 weeks have virtually no chance to survive[14]. The period in between is defined as the 'grey zone of viability'. Decision making in this period of the pregnancy is mostly based on predictions concerning neonatal survival and long-term outcome[15]. The major factor determining survival is gestational age at birth. In the Netherlands the survival rate below 24 weeks' gestation is nihil due to the fact that in general no active neonatal management is started prior to 24 weeks' gestation. International studies show that survival rates increase between 22 and 25 weeks' gestation from 6-37% at 22 weeks to 50-86% at 25 weeks' gestation[16-18] and increases to 80% at 28 weeks' gestation[19]. Other known factors associated with a higher survival rate are birth weight, neonatal sex, ethnicity, corticosteroids for fetal lung maturation and number of fetuses[20,21]. National Dutch guideline on spontaneous extreme preterm birth, is in place to recommend whether or not to start active neonatal management by a neonatologist. Prior to 2006 the limit for active obstetric and neonatal management was 26 weeks' of gestation. After 2006 the recommended limit was 25 weeks' gestation, with an estimated fetal weight of at least 500 grams. In the latest guideline dating September 2010 the recommended limit is 24 weeks' gestation for intubation and ventilation and 25 weeks' for cardiac resuscitation in a shared decision with the parents. Estimated fetal weight is no longer included[22]. Currently, there is no Dutch guideline that addresses iatrogenic or indicated extreme preterm birth.

LEGAL ASPECTS

National regulations

In the Netherlands termination of pregnancy is, subject to a number conditions such as parental request and reflection time, exempted from legal prosecution up to the moment where the newborn is judged to be viable outside the womb. This is usually considered to be after $24^{0/7}$ weeks of gestation for adequately grown fetuses with a sufficient amount of amniotic fluid for lung development and without life threatening congenital disorders[23]. Termination of pregnancy after 24 weeks gestation is primarily not allowed and is punishable by law. However, in cases of life-threatening maternal conditions, termination

of pregnancy could be inevitable in order to save the mother's life. The doctor performing the termination in these cases is exempted from legal prosecution[23]. Recently the regulations have been revised by the ministries of Justice and Health. All terminations of pregnancy for maternal indications have to be reported to an expert-panel of the Dutch Society of Obstetrics and Gynecology for internal audits and registration[24].

International regulations

Legislation and regulations concerning termination of pregnancy for maternal indications differ greatly between countries. In some countries, for example in Thailand or Latin-American countries such as Nicaragua, termination of pregnancy is prohibited at all times, even in cases where the life of the mother is in danger. In other countries, for example Ireland, all countries in the Middle East and many countries in Africa, termination of pregnancy is prohibited, unless the life of the mother is in danger. Other countries, such as Northern America, many countries in Europe and India have more liberal legislation and regulations, and termination of pregnancy is allowed, usually up to a certain gestational age varying from 12 – 28 weeks[25].

ETHICAL ASPECTS

Women with pregnancies complicated by severe maternal illness and threatening maternal death at the limits of fetal viability pose several dilemmas to the professional and the parents alike. Expedited delivery is usually in the best interest of the mother, however this may harm the fetus. Postponing delivery might be in the best interest of the fetus, however this management may increase the likelihood of morbidity and mortality for the mother. Ethical principles that play a role in these decisions are beneficence and nonmalefiscence[15]. Beneficence means the aim to benefit the sick, in these cases the mother. Nonmalefiscence means the aim to do no harm, in these cases to the fetus. Furthermore justice requires that all similar cases should be treated in an equitable way. With these principles in mind, the professional team has, the often, difficult task to counsel the parents on possible management options.

AIMS OF THE THESIS

The aim of this thesis is to provide contemporary information to the professional on termination of pregnancy for maternal indications at the limits of fetal viability, to enable accurate counseling and reduce unwanted practice variation. To reach this aim we investigated:

- The incidence and different indications for termination of pregnancy for maternal indications, at the limits of fetal viability in The Netherlands
- The incidence of termination of pregnancy for hypertensive disorders in the Netherlands.
- The outcomes of subsequent pregnancies, specifically pertaining to the recurrence risk of preeclampsia
- The opinion of Dutch obstetricians and neonatologists regarding management, auditing and reporting cases of termination of pregnancy at the limits of fetal viability.
- The possible differences in maternal and neonatal outcome following immediate delivery versus expectant management in cases of extreme early onset preeclampsia.
- The optimal mode of delivery prior to 28 weeks in case of severe early onset preeclampsia.

OUTLINE OF THE THESIS

Part I focuses on termination of pregnancy for maternal indications without intention to intervene for fetal indications and without active neonatal management:

Chapter 2 presents the results of a retrospective, nationwide cohort study on the incidence and indications of termination of pregnancy for maternal indications at the limits of fetal viability in The Netherlands. **Chapter 3** describes the practice of termination of pregnancy for hypertensive disorders at the limits of fetal viability. Furthermore it addresses the accuracy of fetal weight estimation. In **chapter 4** the outcome of subsequent pregnancies in women with a prior termination of pregnancy for hypertensive disorders is presented. **Chapter 5** describes the results of an online survey amongst Dutch obstetricians and neonatologists about preferences on management, auditing and reporting cases of termination of pregnancy for maternal indications at the limits of fetal viability.

Part II focuses on indicated delivery for hypertensive disorders at the limits of fetal viability with the explicit intention to intervene for fetal indications and active neonatal management:

Chapter 6 describes the results of a retrospective, nationwide Dutch cohort study on the maternal and neonatal outcome in women with preeclampsia with an onset prior to 26 weeks' gestation. **Chapter 7** presents a systematic review concerning the maternal and neonatal outcome in women with preeclampsia with an onset prior to 28 weeks' gestation according to the delivery route.

Chapter 8 presents a new national Dutch protocol on management of termination of pregnancy for maternal indications.

REFERENCES

1. Seri I, Evans J. Limits of viability: definition of the gray zone. Journal of Perinatology 2008: 28, S4–S8
2. Ashimi Balogun OA, Sibai BM. Counseling, management, and outcome in women with severe preeclampsia at 23 to 28 weeks' gestation. Clinical Obstetrics and Gynecology. 2017 Volume 60, Number 1, 183–189
3. Mol BWJ, Roberts CT, Thangaratinam S et al. Pre-eclampsia. Lancet. 2016 Mar 5;387(10022):999-1011
4. Say L, Chou D, Gemmill A et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014 Jun;2(6):e323-33
5. Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. Eur J Obstet Gynecol Reprod Biol. 2013 Sep;170(1):1-7
6. Lisonkova S, Sabr Y, Mayer C, Young C, Skoll A, Joseph KS. Maternal morbidity associated with early-onset and late-onset preeclampsia. Obstet Gynecol. 2014 Oct;124(4):771-81
7. Gaugler-Senden IP, Huijssoon AG, Visser W et al. Maternal and perinatal outcome of preeclampsia with an onset before 24 weeks' gestation. Audit in a tertiary referral center. Eur J Obstet Gynecol Reprod Biol. 2006; 128: 216–221
8. Nardozza LMM, Rabachini Caetano AC, Perez Zamarian AC, Brandão Mazzola J, Pacheco Silva C et al. Fetal growth restriction: current knowledge. Arch Gynecol Obstet. 2017 295:1061–1077
9. Warnes CA. Pregnancy and Delivery in Women With Congenital Heart Disease. Circulation Journal Vol.79, July 2015
10. Swan L. Congenital heart disease in pregnancy. Best Practice & Research Clinical Obstetrics and Gynaecology. 2014;28: 495–506
11. The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC) Endorsed by the European Society of Gynecology (ESG), the Association for European Paediatric Cardiology (AEPC), and the German Society for Gender Medicine (DGesGM). ESC Guidelines on the management of cardiovascular diseases during pregnancy. European Heart Journal 2011 32, 3147–3197
12. Lateef A, Petri M. Managing lupus patients during pregnancy. Best Pract Res Clin Rheumatol. 2013 Jun;27(3):435-47
13. Nevis IF, Reitsma A, Dominic A et al. Pregnancy outcomes in women with chronic kidney disease: a systematic review. Clin J Am Soc Nephrol. 2011 Nov;6(11):2587-98
14. Stoll BJ, Hansen NI, Bell EF, et al. Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates, 1993-2012. JAMA 2015; 314:1039
15. Shinwell ES. Ethics of Birth at the Limits of Viability: The Risky Business of Prediction. Neonatology 2015;107:317–320
16. Anderson JG, Baer RJ, Partridge JC, et al. Survival and Major Morbidity of Extremely Preterm Infants: A Population-Based Study. Pediatrics 2016;138:320154434
17. Ishii N, Kono Y, Yonemoto N, et al. Outcomes of infants born at 22 and 23 weeks' gestation. Pediatrics 2013; 132:62
18. Ancel PY, Goffinet F, et al. Survival and morbidity of preterm children born at 22 through 34 weeks' gestation in France in 2011: Results of the EPIPAGE-2 Cohort Study. JAMA Pediatrics 2015; 169:230
19. Draper ES, Manktelow BN, Cuttini M, et al. Variability in Very Preterm Stillbirth and In-Hospital Mortality Across Europe. Pediatrics. 2017;139(4):e20161990

20. Tyson JE, Parikh NA, Langer J, Green C, Higgins RD, National Institute of Child Health and Human Development Neonatal Research Network. Intensive care for extreme prematurity-moving beyond gestational age. N Engl J Med. 2008;358(16):1672
21. Monier I, Ancel P-Y, Ego A, Guellec I, Jarreau P-H, Kaminski M, Goffinet F, Zeitlin J. Gestational age at diagnosis of early-onset fetal growth restriction and impact on management and survival: a population-based cohort study. BJOG 2017; DOI: 10.1111/1471-0528.14555.
22. richtlijnendatabase.nl/richtlijn/perinataal_beleid_bij_extreme_vroeggeboorte/neonatologische_opvang_bij_vroeggeboorte.html
23. http://wetten.overheid.nl/BWBR0001854/2018-07-01
24. Regeling beoordelingscommissie late zwangerschapsafbreking en levensbeëindiging bij pasgeborenen. Staatscourant Nr. 3145 26 januari 2016
25. www.womenonwaves.org

Part I

Termination of pregnancy for maternal indications without intention to intervene for fetal indications and without active neonatal management

Chapter 2

Termination of pregnancy for maternal indications at the limits of fetal viability; a retrospective cohort study in the Dutch tertiary care centers

Eerden L van , Zeeman GG, Page-Christiaens GCM, Vandenbussche F, Oei SG, Scheepers HCJ, Eyck J van, Middeldorp JM, Pajkrt E, Duvekot JJ, Groot CJM de and Bolte AC

BMJ Open 2014;4:e005145

ABSTRACT

Objective

Maternal morbidity, either pregnancy-related or pre-existent can become life-threatening and of such severity to warrant termination of pregnancy (TOP). In this situation chances of fetal survival are usually poor, either because of low gestational age, and/or because of the fetal effects of the maternal condition. Examples include severe growth restriction in pre-eclampsia and intra-uterine infection due to very early preterm prelabor rupture of membranes. There are very few reports on the prevalence of termination of pregnancy for maternal indication at the limits of fetal viability. We investigated the prevalence and indications for TOP on maternal indication in the ten tertiary care centers in the Netherlands during the past decade.

Study design

We conducted a retrospective review of the medical records of all women who underwent TOP for maternal indications between 22 to 27 completed weeks of gestation in all 10 tertiary care centers from 2000 to 2009.

Results

During the study period there were 1,929,470 deliveries. 163,052 (8.4%) of these took place in one of the ten tertiary care centers and 177 pregnancies were terminated for severe maternal disease, 131 for hypertensive disorders, 29 for intra-uterine infection and 17 for other reasons. The mean gestational age at TOP was 171 days (243/7 weeks) ± 10 days. No maternal deaths were recorded. The overall perinatal mortality was 99,4%.

Conclusion

Over a ten year period TOP for maternal indications was performed in 1 in 1000 deliveries in the 10 Dutch tertiary care centers. Hypertensive disorders comprised three quarters of cases.

INTRODUCTION

Indications for termination of pregnancy in the Netherlands can be divided in: psychosocial reasons (unwanted pregnancies), genetic reasons (fetus with congenital abnormalities) and maternal medical disorders including psychiatric disorders. Under Dutch legislation, in place and unchanged since 1981, termination of pregnancy (TOP) is possible up to the gestational age where a newborn can survive outside the womb. This is currently considered $24^{0/7}$ weeks for adequately grown fetuses without lethal disorders and a sufficient amount of amniotic fluid for lung development[1]. Annually there are approximately 28000 terminations of pregnancy between 5 and 24 weeks in the Netherlands. Termination for social indications up to 22 weeks is performed in clinics with a special license. Terminations for genetic reasons and for medical maternal reasons are performed in obstetric units of secondary or tertiary care centers.

In case of lethal fetal disorders such as trisomy 18, 13 or triploidy termination is also allowed beyond 24 weeks, provided a number of criteria are fulfilled[2]. These cases are audited by a committee of the Dutch Society of Obstetrics and Gynecology. Termination for severe fetal disorders in case of dismal, but not necessarily lethal, prognosis for the fetus may be excepted from legal prosecution provided adherence to stringent criteria and after assessment by an expert committee appointed by the ministries of Health and Justice. This committee consists of an obstetrician, a paediatrician and an ethicist, and is chaired by a lawyer[2]. This committee reports directly to the Attorney General, the highest legal authority in The Netherlands. Termination of pregnancy beyond 24 weeks' gestation for life - threatening maternal conditions in combination with dismal fetal prospects (e.g. due to severe growth restriction or anhydramnios) are generally not reported, since termination of pregnancy in such cases is considered inevitable and the only justifiable management option to prevent deteriorating maternal morbidity or even mortality. According to the Guideline on Late Termination of Pregnancy of the Dutch Society of Obstetrics and Gynecology maternal indications that warrant TOP include, but are not limited to: hypertensive disorders with organ dysfunction, sepsis, severe exacerbation of auto-immune disorders, severely deteriorating cardiac function, transplant rejection, rapidly progressing malignancies as well as life-threatening major obstetric haemorrhage[2]. In these situations the fetus is also compromised, either because of the gestational age, and/or because of the low estimated fetal weight[3]. Termination of pregnancy beyond 24 weeks' gestation for these indications is considered to be extremely rare. The guideline on termination of pregnancy from the Dutch Society of Gynaecology and Obstetrics states that these patients should be referred to and treated in a tertiary care centre. Termination of pregnancy for maternal indications is only performed after extensive multidisciplinary consultation[2].

The literature lacks reports on the prevalence of termination of pregnancy for maternal indication at the limits of fetal viability. The gestational age and estimated fetal weight to consider "active perinatal management" directed towards survival have recently been lowered to 24 weeks and 500 grams in many countries, including the Netherlands. We aimed to investigate the prevalence of and indications for TOP in severely sick mothers, at the limits of fetal viability in the Netherlands between 2000 and 2009.

METHODS

We conducted a retrospective review of the medical records of all women who had TOP for maternal indications between 22 and 27 completed weeks of gestation in the 10 Dutch tertiary care centers from 2000 to 2009. Cases were identified using local delivery databases. In all cases the fetus was judged to be non-viable, either because of the gestational age or because of the impact of maternal disease on the prospects for the fetus, e.g. severe growth restriction. The inclusion and exclusion criteria are listed in table 1.

Inclusion criteria	Gestational age $22^{0/7}$ – $28^{0/7}$
	Severe maternal condition reason for termination
	Live fetus at onset of termination
	No fetal monitoring
	No interventions aimed at fetus
Exclusion criteria	Gestational age ≤ $21^{6/7}$ or ≥ $28^{1/7}$
	Fetal indication for termination
	Fetal demise at onset of termination

Table 1. Inclusion and exclusion criteria for this study

Data extraction from the original medical files was performed by the first or the last author (LvE and ACB) in all cases. Data on the total number of deliveries in the 10-year period were extracted from The Netherlands Perinatal Registry (PRN foundation). The indication TOP for maternal indication is not registered in this registry[4].

The study design was reviewed and approved by the medical ethics committee of the VU Medical Center in Amsterdam.

RESULTS

In the ten year study period there were 1,929,470 deliveries in the Netherlands of which 163,052 (8.4%) took place in the 10 tertiary care centers[5,6]. Of those 11474 deliveries occurred between $22^{0/7}$ and $27^{6/7}$ weeks of gestation. A total of 177 (1,5%) fulfilled the inclusion criteria, 172 singleton and 5 twin pregnancies. TOP was performed for

hypertensive disorders and preterm prelabor rupture of membranes (PPROM) with intra-uterine infection in 131 (74%) and 29 (16%) cases, respectively. In 17 cases (9%) there was another motive to terminate the pregnancy (figure 1).

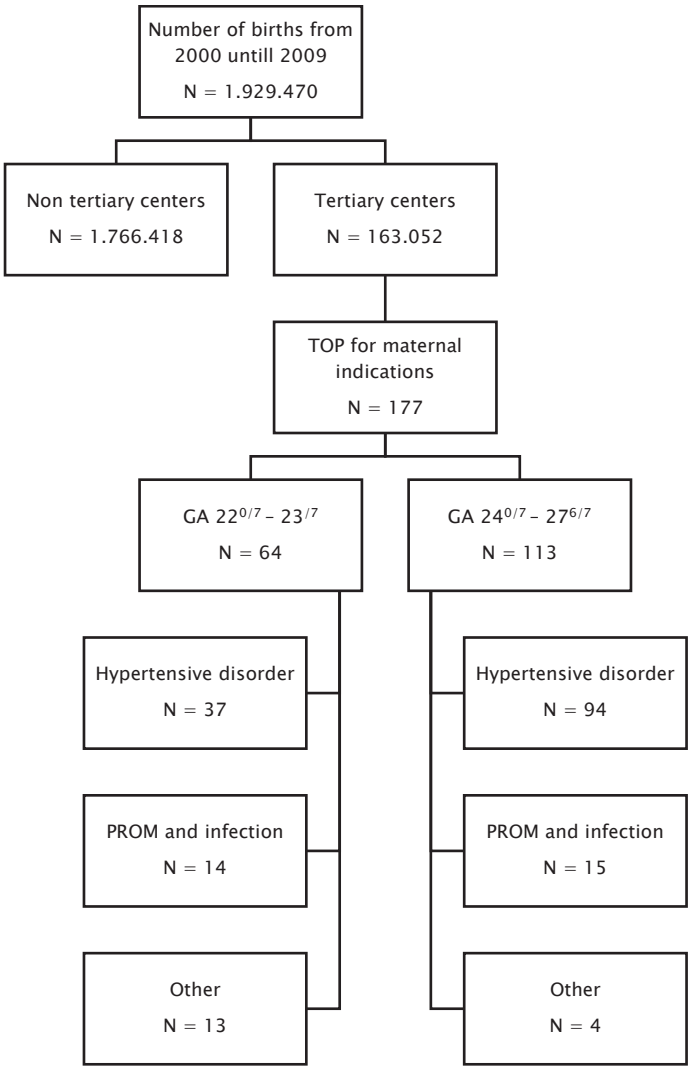


Figure 1. Flowchart Patient selection. TOP = termination of pregnancy, GA = gestational age, PROM = prelabor rupture of membranes

The mean gestational age at TOP was 171 days (24$^{3/7}$) weeks + 10 days. In the hypertension group the mean gestational age was 173 days (24$^{5/7}$) ± 9.7 days as compared to 167 days (23$^{6/7}$) ± 10.1 days in the infection group and 162 days (23$^{1/7}$) ± 7.0 days for

the other indications. The gestational age at termination was significantly higher in the hypertension group (173 days ± 9.7 days) compared to the infection group (167 days ± 10.1 days) (p= 0.006). This also applied to the hypertension group (173 days ± 9.7 days) compared to the other indications (162 days ± 7.0 days) (p<0.001).

There were no cases of maternal mortality. A total of 182 neonates were born. There was one unexpected survivor born at GA $25^{5/7}$ weeks' gestation with a birth weight of 600 grams. This pregnancy was terminated without fetal heart rate monitoring for severe HELLP syndrome using intravenous sulprostone. The child is now four years old and has a normal development so far.

The number of pregnancies terminated beyond the limit of $24^{0/7}$ weeks' gestation was 113 (64%). In 94 of these cases (83%) pregnancy was terminated for a severe hypertensive disorder. Fifteen pregnancies (13%) were terminated for overt intra-uterine infection in the setting of PPROM and four pregnancies (3.5%) for other indications (table 2).

Indication	GA < 24 weeks (%)	GA > 24 weeks (%)
Overall	64	113
Hypertensive disorders	37 (58%)	94 (83%)
Intra-uterine infection	14 (22%)	15 (13%)
Other		
• Uterine rupture	1 (1.6%)	1 (0.8%)
• Obstetric bleeding	3 (4.7%)	2 (1.7%)
• Heart failure	3 (4.7%)	1 (0.8%)
• Psychiatric disorders	3 (4.7%)	
• Malignancy	3 (4.7%)	

Table 2. Indications for termination of pregnancy. GA = gestational age

In cases of termination beyond 24 weeks a multidisciplinary team, consisting of at least obstetricians, neonatologists and other specialists, when indicated, discussed the intended advise for termination of pregnancy and examined alternative options before coming to a final advise to the parents.

Labor was induced with prostaglandins in 176 (99.4%) of the cases. In one case dilatation and evacuation was performed after feticide with potassium chloride. After induction two pregnancies were terminated by caesarean section. In one case a caesarean section was performed to expedite delivery because of recurrent eclamptic fits with neurological impairment. In the other case a caesarean section was performed because of an uterine rupture accompanied by a hypovolemic shock.

In 2006 a national guideline on active perinatal and neonatal management after spontaneous preterm birth at the limits of fetal viability was introduced. Before 2006, active management was generally started at 26 weeks' gestation, whereas this was lowered to 25 weeks' gestation in the guideline. The introduction of this guideline has had no major

effect on the number of TOP for maternal indications. Figure 2 shows the number of TOP per year.

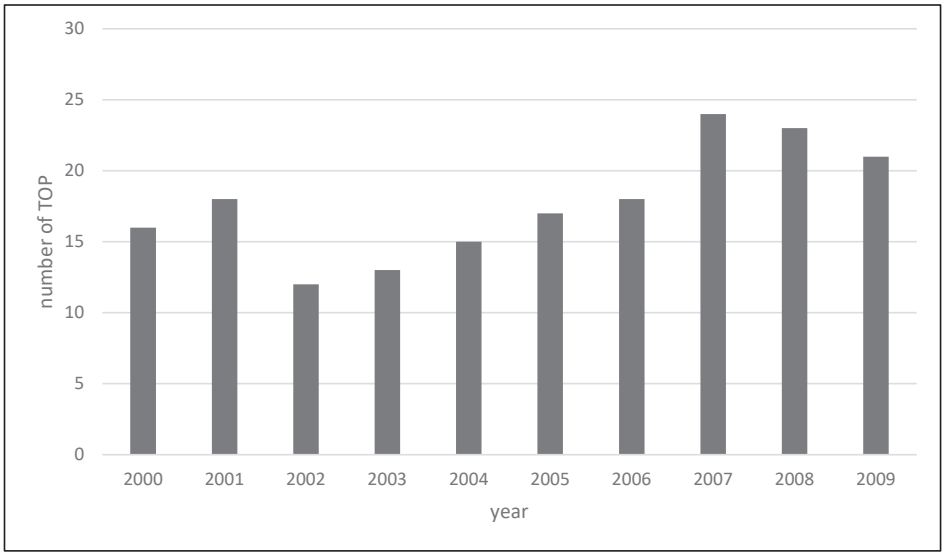


Figure 2. Number of TOP per year

The incidence of TOP varied substantially between different centers (table 3).

Centre	Deliveries	Terminations	Incidence (‰)	GA at start active fetal management
1	19082	47	2.46	$26^{0/7}$
2	15861	33	2.08	$26^{0/7}$
3	18468	27	1.46	$25^{0/7}$
4	13391	19	1.41	$25^{0/7}$
5	14551	18	1.23	$26^{0/7}$
6	11830	9	0.76	$24^{0/7}$
7	16387	9	0.54	$26^{0/7}$
8	19523	6	0.30	$25^{0/7}$
9	19748	5	0.25	$24^{0/7}$
10	14211	4	0.28	$26^{0/7}$
	163052	**177**		

Table 3. Overview of terminations per center and policy of active fetal management in the period 2000-2009. GA = gestational age

Two exemplary cases:

Case 1: a nulliparous woman, with an unremarkable history, developed severe pre-eclampsia with progressive HELLP syndrome at a gestational age of 23 weeks and 2 days. She was admitted and was treated with multiple intravenous antihypertensive drugs and magnesium sulphate. Ultrasound showed an estimated fetal weight of 480 grams. She was counselled for termination of pregnancy due to the early gestational age and the progressive course of the disease and delivered a stillborn girl of 470 grams (<p10) at 24 weeks' gestation. The delivery took place on the intensive care unit due to refractory hypertension and pulmonary oedema in the mother.

Case 2: a woman in her fourth pregnancy was admitted at a gestational age of 22 weeks. Her obstetric history revealed dilated peripartum cardiomyopathy. Pre-conceptionally, she had been strongly advised against pregnancy. She was admitted to the ICU because of severely deteriorating cardiac function. After extensive counselling by a multidisciplinary team consisting of obstetricians, cardiologists and neonatologists the pregnancy was terminated at 22 weeks and 4 days' gestation. She delivered a stillborn son.

COMMENT

In the period 2000-2009 we identified 177 cases of TOP for life-threatening maternal morbidity in the ten tertiary care centers in the Netherlands. Since the indication for termination of pregnancy is not specified in the Netherlands Perinatal Registry nor in the legally required national report on termination of pregnancy, it is not possible to check our data for underreporting. However, because the guideline on late termination of pregnancy from the Dutch Society of Gynecology and Obstetrics states that women should be referred to and treated in a tertiary care centre in case of severe maternal morbidity, we assume that we found most cases of TOP for maternal indications.

We found that there was a difference in incidence of TOP between the tertiary care centers. This may, amongst others, be due to different local interpretation on active neonatal management at the limits of viability in a period where thresholds for active management were subject to gradual change (see table 3). It is possible that some centers advised to continue the pregnancy anticipating an intra-uterine fetal demise within days.

Dutch guidelines are in place to recommend whether or not to start active neonatal management by a neonatologist in cases with spontaneous preterm labor and an expected weight appropriate for gestational age. These guidelines are periodically revised based on current (inter)national practice standards. Prior to 2006 the overall limit for active obstetric and neonatal management was 26 weeks' of gestation. After 2006 the

recommended limit was 25 weeks' gestation, with an estimated fetal weight of at least 500 grams[7]. In the latest guideline dating September 2010, which was introduced after the inclusion period of this study, the recommended limit is 24 weeks' gestation for intubation and ventilation and 25 weeks for cardiac resuscitation. Estimated fetal weight limits are no longer included[8].

The prospects of children born at 24-25 weeks are nevertheless poor, even with active management. A recent report showed that infants who received active perinatal and neonatal management survived in 43% of cases at 24 weeks' and in 61% of cases at 25 weeks'. Severe short term neonatal morbidity was registered in 70-80% of surviving children[9]. In case of severe maternal morbidity in pregnancy, the prospects for an intact survival for the fetus are considered to be even worse due to the combination of a low gestational age and, in most cases, severe growth restriction or fetal inflammatory response syndrome, as well as the deleterious effects of the underlying maternal condition, such as chronic fetal hypoxia. In case it becomes inevitable for the mother's sake to terminate the pregnancy at the limits of fetal viability, this expected extremely poor outcome of the child does not support an active fetal/neonatal management. A caesarean section puts the mother at even higher short term and long term risks. Therefore, termination via induction of vaginal delivery with prostaglandins and without fetal monitoring will often be the safest policy.

Hypertensive disease comprised three quarters of the cases and was the indication for termination in 83% of the terminations beyond 24 weeks. Experts in the field as well as the WHO and NICE guidelines on hypertensive disorders in pregnancy, recommend that women who develop severe pre-eclampsia at less than 23 weeks should be counselled towards termination of pregnancy[10-12]. Gaugler et al describe 26 pregnancies, complicated by pre-eclampsia with an onset before 24 weeks' gestation and managed expectantly. The overall perinatal mortality was 82%, with major maternal morbidity in 65% of the women[13].

In 16% of overall cases and 13% of cases beyond 24 weeks, the indication for terminating pregnancy was intra-uterine infection with overt or threatening maternal sepsis. Septic shock and maternal death have been reported in pregnancies managed conservatively[14-16]. Therefore, termination of pregnancy is recommended in case of serious clinical infection[15].

In 9% of overall cases and 3,5% of cases beyond 24 weeks pregnancy was terminated for other reasons. In the international literature papers on other reasons for pregnancy termination for maternal indications are scarce. One study from Australia mentions psychiatric disorders, malignancies and cardiac disorders as the most common maternal indications for termination between 5 – 23 weeks' gestation[17]. In a recent paper by Piel et al from 4 hospitals in the Parisian area covering 95000 deliveries between 2001 and 2010 the main reasons for terminating pregnancy for maternal reasons between 5 and

23 weeks of gestation were (in decreasing order of frequency): pre-eclampsia, malignancies, drug addiction, AIDS, risk of suicide, psychosis, rape, pre-existing maternal somatic or psychiatric diseases, uterine bleeding or risk of uterine rupture[18].

What can we learn from our observations? There are conditions where maternal health and life are compromised to such a degree, whilst chances for healthy fetal survival so dismal, that termination of pregnancy is inevitable. This entails pregnancy-induced conditions such as pre-eclampsia and HELLP syndrome, intra-uterine infection and obstetric haemorrhage, but also pre-existing or coincidental maternal conditions such as cardiac failure or malignancies. Counselling towards termination of pregnancy in these situations is the result of a multidisciplinary perinatal team discussion involving neonatologists, and a shared decision with the mother and her partner.

We suggest that the indication for termination of pregnancy becomes a mandatory item in the Netherlands Perinatal Registry. This will gain insight in the prevalence of TOP for maternal indications. Furthermore this registration will enable audits of these cases by a medical peer-group.

CONCLUSION

(Inter)national literature on termination of pregnancy for maternal indication at the limits of fetal viability is scarce. In this retrospective cohort we found a prevalence of 0.1% of termination of pregnancy for maternal reasons in the ten tertiary care centers in The Netherlands between 2000-2009.

REFERENCES

1. www.wetboek-online.nl/wet/Sr/82a.htlm
2. NVOG modelprotocol LZA: Medisch handelen late zwangerschapsafbreking 2007. Available at http://nvog-documenten.nl/index.php
3. Seri I, Evans J. Limits of viability: definition of the gray zone. Journal of Perinatology 2008;28:S4-S8
4. www.perinatreg.nl/home_english
5. LVR. Landelijke Verloskundige Registratie (Dutch Perinatal Database): The Netherlands Perinatal Registry, Prismant. Prismant
6. Centraal Bureau voor de Statistiek, Den Haag/Heerlen.
7. NVOG nota verwijzing naar een perinatologische centrum. Available at www.nvog-documenten.nl/index.php
8. Nederlandse richtlijn perinataal beleid bij extreme vroeggeboorte. Available at www.nvog-documenten.nl/index.php
9. de Kluiver E, Offringa M, Walther FJ, Duvekot JJ, de Laat MW. [Perinatal policy in cases of extreme prematurity; an investigation into the implementation of the guidelines] [article in Dutch]. Ned Tijdsch Geneeskd. 2013;157(38):A6362
10. Sibai BM, Barton JR. Expectant management of severe preeclampsia remote from term: patient selection, treatment, and delivery indications. Am J Obstet Gynecol 2007;196:514.e1-9
11. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia, World Health Organization 2011. Available at http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/9789241548335/en/index.html
12. The management of hypertensive disorders during pregnancy. NICE guideline CG107, august 2010. Available at http://guidance.nice.org.uk/CG107
13. Gaugler-Senden IPM, Huijssoon AG, Visser W, Steegers EAP, de Groot CJM. Maternal and perinatal outcome of preeclampsia with an onset before 24 weeks' gestation. Audit in a tertiary referral center. European J Obstet Gynecol 2006;128:216-221
14. Waters TP, Mercer BM. The management of preterm premature rupture of membranes near the limit of fetal viability. Am J Obstet Gynecol 2009;201(3):230
15. Moretti M, Sibai BM. Maternal and perinatal outcome of expectant management of premature rupture of membranes in the midtrimester. Am J Obstet Gynecol 1988;159(2):390
16. Yang LC, Taylor DR, Kaufman HH, Hume R and Calhoun B. Maternal and fetal outcomes of spontaneous preterm premature rupture of membranes. J Am Osteopath Assoc 2004;104:537-42
17. Barrett HL, Lust K, Callaway LK, Fagermo N, Portmann C. Termination of pregnancy for maternal medical indications: Failings in delivery or contraceptive advice? Aust N Z J Obstet Gynaecol 2011 Dec;51(6):532-6
18. Piel B, Azria E, Oury JF, Carbillon L, Mandelbrot L. [Terminations of pregnancy for maternal indications in the Paris area: a retrospective multicenter study in the period between the 2001 French law on termination of pregnancy and the new bioethics law][article in French]. J Obstet Biol Reprod (Paris) 2013 Jun;42(4):342-50

Chapter 3

Terminating pregnancy for severe hypertension when the fetus is considered non-viable: a retrospective cohort study

L van Eerden, MF van Oostwaard, GG Zeeman, GCM Page-Christiaens, E Pajkrt, JJ Duvekot, FP Vandenbussche, SG Oei, HCJ Scheepers, J van Eyck, JM Middeldorp, SV Koenen, CJM de Groot and AC Bolte

Eur J Obstet Gynecol Reprod Biol. 2016 Nov;206:22-26

ABSTRACT

Objective

To investigate frequency and practise of termination of pregnancy for early-onset hypertensive disorders where the fetus is considered to be non-viable.

Study Design

Retrospective cohort study in all Dutch tertiary perinatal care centers (n=10), between January 2000 and January 2014. All women who underwent termination of pregnancy, without fetal surveillance or intention to intervene for fetal reasons, for early-onset hypertensive disorders in pregnancy, were analysed. Women eligible for this study were identified in the local delivery databases. Medical records were used to collect relevant data.

Results

Between January 2000 and January 2014, 2.456.584 women delivered in The Netherlands, of which 238.448 (9.7%) in a tertiary care centre. A total of 161 pregnancy terminations (11-12 per year) for severe early-onset preeclampsia were identified, including 6 women with a twin pregnancy. Mean gestational age at termination was 172 days (GA $24^{4/7}$) ± 9.4 days. In 70% of cases termination was performed at or shortly after 24 weeks' gestation. 74.5%% of women developed HELLP syndrome (n=96), eclampsia (n=10) or needed admission to an ICU (n=14). Birth weight was below 500 grams in 64% of cases. In 69% of the cases the estimated fetal weight was within a 10% margin of the actual birth weight.

Conclusion

Termination of pregnancy for early-onset hypertensive disorders without intervention for fetal indication occurs approximately 12 times per year in The Netherlands. More data is needed to investigate contemporary best practice regarding termination of pregnancy for early-onset hypertensive indications at the limits of fetal viability. Considering the frequency of maternal complications termination of pregnancy and not expectant management should be considered for all women presenting with severe early onset hypertensive disorders at the limits of fetal viability.

INTRODUCTION

The incidence of severe early onset preeclampsia (PE) is increasing worldwide[1]. Preeclampsia is annually accountable for approximately 60.000 maternal deaths worldwide. Cerebral complications, such as eclampsia and intracranial haemorrhage account for at least 75% of these[2]. In situations where maternal health is severely compromised and where prognosis for intact fetal survival is virtually non-existent due to early gestational age complicated by severe growth restriction, termination of pregnancy may be considered[3-5,10]. In an authorative review, Sibai et al. describe a maternal complication rate of 57%, and an overall fetal mortality rate of 83% when early-onset preeclampsia is managed expectantly. The authors therefore state that in case of severe preeclampsia before 24 weeks, termination of pregnancy should be seriously considered in order to prevent severe maternal morbidity or mortality[5].

The overall frequency and indications for termination of pregnancy for maternal indications were recently described by our group[7]. In the current manuscript we analyzed in more detail the group of women who presented with early-onset hypertensive disorders.

Aim of this study is to gain insight in Dutch practice patterns of all cases of termination of pregnancy for early-onset hypertensive disorders in pregnancies were the fetus is considered non-viable over the last 15 years. Secondarily, we aimed to investigate the accuracy of fetal weight estimation on which fetal prognosis was based.

METHODS

We performed a Dutch nationwide retrospective audit of all cases of termination of pregnancy for early-onset hypertensive disorders in pregnancies considered non-viable between January 2000 and January 2014. All women who underwent termination of pregnancy because of severe maternal hypertensive disorders between 22 and $27^{6/7}$ weeks of pregnancy in tertiary care centers were included. In all cases the fetus was considered to be non-viable, either because of the gestational age and/or because of severe growth restriction. According to Dutch guidelines, valid during the study period, a fetus at a gestational age of less than 24 weeks was considered non-viable[13]. Exclusion criteria were termination of pregnancy for other maternal indications, fetal congenital anomalies or intra-uterine fetal demise. Termination of pregnancy was defined as termination of a vital pregnancy and intention of primary non-intervention for fetal indications. All pregnancies were terminated using prostagladins (i.e. intravenous sulprostone or misoprostol).

Recruitment was limited to the tertiary care centers (n = 10), because according to current practice and the Dutch Society of Obstetrics and Gynaecology guideline on hypertensive disorders in pregnancy, women who develop preeclampsia prior to 32 weeks' gestation should be referred to and treated in a tertiary care center. These centers are

equipped with a maternal obstetric high care unit as well as a Neonatal Intensive Care Unit (NICU)[8,19]. Cases were identified through a search in the local delivery databases. To control for potential underreporting, we cross-checked the prevalence data with the Netherlands perinatal registry (PRN-registry)[9]. Relevant demographic and clinical data were extracted from the medical records and transferred to a standardized data collection form. Demographic data included maternal age at termination, parity, and medical and obstetric history. Clinical data included information about the index pregnancy and delivery including gestational age at admission, gestational age at delivery, birth weight and gender. Furthermore, specific data used for clinical decision making were recorded; gestational age, the last estimated fetal weight (EFW) prior to termination and suspected growth restriction (EFW < 10th percentile).

Definitions of preeclampsia and HELLP syndrome were derived from the guidelines of the International Society for the Study of Hypertension in Pregnancy (ISSHP)[11] and the NICE guideline Hypertension in Pregnancy[12]. Severe preeclampsia is defined as hypertension (diastolic blood pressure ≥110 mmHg or systolic blood pressure ≥160 mmHg on two occasions) in combination with proteinuria (defined as a protein/creatinine ratio of ≥30 mg/mmol in a random sample or a urine protein excretion of ≥300 mg per 24 hrs) and one or more of the following; oliguria, cerebral or visual disturbances, pulmonary edema, epigastric or upper-quadrant pain, impaired liver function, thrombocytopenia or fetal growth restriction, after 20 weeks of pregnancy. Severe maternal morbidity was defined as HELLP syndrome (haemolysis (elevated lactate dehydrogenase (LDH) levels ≥ 600 U/L), elevated liver enzymes by levels of aspartate transaminase (ASAT) ≥ 70 U/L or alanine transferase (ALAT) ≥ 70 U/L and low platelets < 100,000/mm), eclampsia or admission to an ICU.

Statistical analysis was performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as means with standard deviations (SD). We compared estimated fetal weight by ultrasound and actual birthweight. Differences between the groups were tested with a parametric (unpaired t-test) test as appropriate. P value less than 0.05 was considered to indicate statistical significance.

An acknowledged ethical advisory board approved the study (VUmc # 29-2010/200).

RESULTS

Between January 2000 and January 2014, 2.456.584 women delivered in The Netherlands, of which 238.448 (9.7%) in a tertiary care center. Pregnancy was terminated for early-onset preeclampsia in 161 women (6.5 per 100.000). Among these, 6 women had a twin pregnancy. A cross-check with the Netherlands Perinatal Registry demonstrated that 100% of the cases were identified[9].

Maternal characteristics and outcome are shown in table 1.

	Mean (SD) or N (%)
Age (y)	30.6 (5.2) N=161
Parity	
Nulliparous (no pregnancies > GA 16 weeks)	**116** (72)
1 foetal loss < 16 weeks	21 (18)
2 or more foetal losses < 16 weeks	8 (6.9)
Multiparous	**45** (28)
Total number of previous pregnancies	100
Live offspring	57 (57)
Previous perinatal death	15 (15)
previous termination for maternal indication	2
Foetal loss < 16 weeks	15 (33)
Previous PE or HELLP	14 (31)
Previous preterm delivery	13 (62)
Previous term delivery	24 (53)
Medical History *	
No preexisting disease	**82 (51)**
nulliparous	*61*
multiparous	*21*
Chronic Hypertension	**33 (21)**
Nulliparous	*23*
Multiparous	*10*
Trombofilia**	**10 (6.2)**
Nulliparous	*5*
Multiparous	*5*
Kidney disease	**5 (3.1)**
Nulliparous	*3*
Multiparous	*2*
Other***	**16 (10)**
Nulliparous	*11*
Multiparous	*5*
Gestational age at onset of termination (weeks)	$24^{4/7}(22^{0/7} - 27^{6/7}) \pm 9.4$ days
22-23$^{6/7}$ weeks	48 (30)
24-25$^{6/7}$ weeks	84 (52)
≥ 26$^{0/7}$ weeks	29 (18)
Maternal outcome	
Maternal death	**-**
HELLP syndrome	**95 (59)**
Eclampsia	**10 (6.2)**
Admission to ICU****	**14 (8.4)**

Table 1. Maternal characteristics and outcome. Continuous data are presented as means (SD) or N (%)
* several women had more than one relevant condition in their history
**Thrombophilia: antiphospholipid syndrome, protein S deficiency, Factor V Leiden mutation
***Other: SLE, diabetes mellitus, Crohn's disease, haemoglobinopathy, malignancy
****Admission to ICU includes women with pulmonary edema, refractory hypertension, eclampsia, heart failure and hypovolemic shock

The mean maternal age was 31 years and 116/161 were nulliparous (72%). The medical history was unremarkable in 82/161 women (51%).

The mean gestational age at termination was 172 days ($24^{4/7}$ weeks) ± 9.4 days. Ninety-two women (57%) were admitted at a gestational age of less than 24 weeks. In 23/92 women (25%), induction of labor was commenced immediately after initial stabilization. In the remaining 69/92 women (75%) pregnancy management was initially expectant. The mean interval between admission and start of termination was 9.3 days ± 5.4 days.

In 113/161 women (70%) termination was started at or beyond 24 weeks (mean GA $25^{2/7}$ ± 9.4 days). In these cases a multidisciplinary team, consisting of at least obstetricians, neonatologists, discussed the case and examined alternative options before providing a recommendation to the parents. The main reason to terminate a pregnancy after 24 weeks' gestation was rapid maternal deterioration, such as the development of progressive HELLP syndrome, eclampsia or refractory hypertension.

No maternal deaths were recorded. One patient with a uterine scar from a previous caesarean section underwent an emergency caesarean section after administration of prostaglandins because of uterine rupture and hypovolemic shock.

Table 2 shows the neonatal characteristics.

Neonatal outcome	**Mean**	**N = 167** **n (%)**
Sex		167
Male		60 (36)
Female		99 (59)
Unknown		8 (4.9)
Perinatal mortality		166 (99.6)
Birth weight (grams)	460 ± 103 g	
>10th percentile		36 (23)
<10th percentile		125 (78)
<5th percentile		106 (66)
Unknown		6 (3.5)

Table 2. Neonatal outcome

Data of 167 neonates are available, originating from 155 singleton and 6 twin pregnancies. The mean birth weight for the entire cohort was 460 grams ± 103 grams. Birth weight was below 500 grams in 64% of cases. In 145 neonates estimated fetal weight based on antenatal ultrasound parameters was recorded. The interval between measurement of EFW and day of birth was 5.4 days ± 2.1 days. In 69% of the cases the EFW was within a 10% margin of the actual birth weight. In 25 cases (22%) the EFW was more than 10% underestimated and in 10 cases (9%) the EFW was more than 10% overestimated (table 3).

Gestational age at termination	Neonates (N)	Prenatal EFW N (%)	Birth weight N (%)
22^0 - 22^6	22	< 500 g: 20 (100)	< 500 g: 21 (100)
		≥ 500 g: -	≥ 500 g: 0
		Unknown: 2	Unknown: 1
23^0 - 23^6	28	< 500 g: 19 (90)	< 500 g: 24 (100)
		≥ 500 g: 2 (10)	≥ 500 g: 0
		Unknown: 7	unknown: 4
24^0 - 24^6	43	< 500 g: 29 (71)	< 500 g: 27 (64)
		≥ 500 g: 12 (29)	≥ 500 g: 15 (36)*
		Unknown: 2	unknown: 1
25^0 - 25^6	45	< 500 g: 21 (51)	< 500 g: 23 (51)
		≥ 500 g: 20 (49)	≥ 500 g: 22 (49)**
		Unknown: 4	
26^0 - 26^6	23	< 500 g: 5 (26)	< 500 g: 7 (30)
		≥ 500 g: 14 (74)	≥ 500 g: 16 (70)***
		Unknown: 4	
27^0 - 27^6	6	< 500 g: 2 (33)	< 500 g: 1 (17)
		≥ 500 g: 4 (66)	≥ 500 g: 5 (83)****
		Unknown: -	

Table 3. Estimated foetal weight(EFW) and actual birth weight, according to gestational age in weeks. Percentages are shown according to the number of available records
* mean 560 grams ± 117 grams
** mean 593 grams ± 117 grams
*** mean 612 grams ± 122 grams
**** mean 578 grams ± 121 grams

In the 113 pregnancies that were terminated at or beyond 24 weeks, the mean EFW was 495 grams ± 113 grams, while the mean actual birth weight was 508 grams ± 117 grams (mean difference between EFW and birth weight: 13.3 gram 95%CI: - 24.30 to – 2.30 p = 0.018).

Figure 1 shows the EFW and birth weight per neonate.

The decision to refrain from fetal monitoring and interventions for fetal indication was guided by poor fetal prognosis, based on: gestational age, EFW (51% < 500 grams), suspected growth restriction (73% EFW < 10th percentile), lack of growth between 2 assessments, abnormal Doppler profiles and the amount of amniotic fluid.

The perinatal mortality was 99.6%. One baby girl was born alive and admitted to the NICU. After 4 years of follow up she has a normal development. The pregnancy was terminated for severe HELLP syndrome using intravenous sulprostone at a GA of $25^{5/7}$ weeks. Ultrasound prior to termination showed growth restriction and oligohydramnios and an EFW of 550 grams. The birth weight was 600 grams (16th percentile).

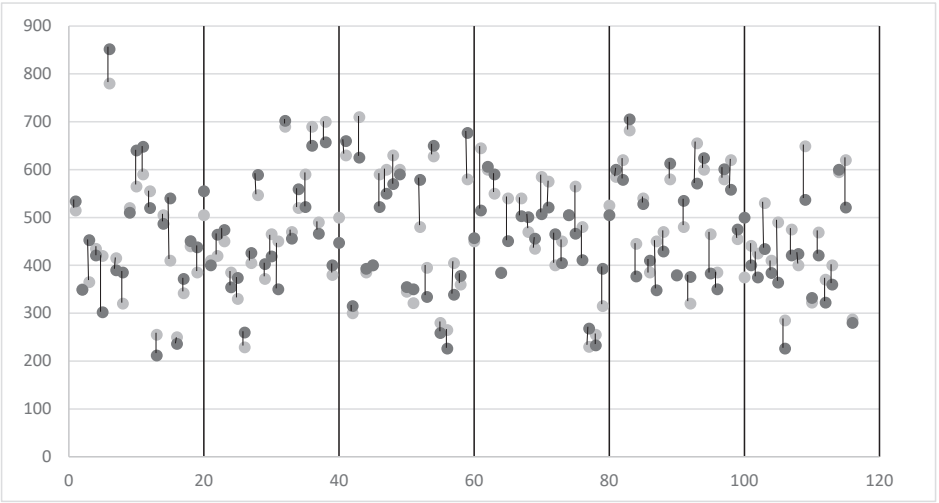


Figure 1. Estimated fetal weight and actual birth weight per case. X-axis: case number, Y-axis: estimated fetal weight (black dot) and actual birth weight (grey dot) joined by a line.

The number of terminations per center per 10,000 deliveries varied from 2.1 per 10,000 deliveries in one center to 17.2 per 10,000 deliveries in another center.

COMMENT

Main findings:

Between 2000 and 2014, 161 women underwent termination of pregnancy for early-onset hypertensive disorders when the fetus was considered non-viable (6.5/100,000). The main reason to terminate was rapid maternal deterioration (progressive HELLP syndrome, eclampsia or refractory hypertension). In 75% management was initially expectant. 75% of women developed HELLP syndrome, eclampsia or needed admission to an ICU. In the majority of women (70%) termination was performed at or beyond 24 weeks. For the decision to refrain from fetal monitoring and active neonatal support the following parameters were taken into consideration: gestational age, estimated fetal weight, growth restriction, and lack of interval growth. In 31% of the cases EFW was more than 10% underestimated or overestimated compared to the actual birth weight. All terminations were performed medically.

Strengths and weaknesses:

This study describes a large nationwide cohort, considering the rareness of the condition. These data fill a knowledge gap concerning the frequency of termination of pregnancy for hypertensive disorders and concerning factors contributing to the decision to do so.

Furthermore, detailed medical history and outcome information is available since data was gathered from the medical records. During the study period national guidelines for management of pre-eclampsia remained unchanged[8,19].

The most important limitation is that this is a retrospective study. We did however made a major effort to ensure completeness of cases.

Interpretation:

Gestational age and fetal growth:

In this cohort, 57% of women were admitted prior to a gestational age of 24 weeks'. Despite international literature and guidelines, stating that such women should be counselled towards termination, 75% of these pregnancies were initially managed expectantly and prolonged with 9.3 days on average. Expectant management resulted in significant maternal deterioration such that termination was considered inevitable.

In women who develop severe early-onset preeclampsia between $24^{0/7}$ and $32^{6/7}$ weeks' gestation, obstetric management will depend on prospects for intact survival of the infant[3-5]. This study presents a cohort that progressed beyond 24 weeks where disease severity and non-viable prognosis for the fetus led to the difficult decision to terminate the pregnancy precluding infant survival. In these cases prolongation of pregnancy with a risk of severe maternal complications but also a potential increase in number of surviving infants was weighed against termination of pregnancy with probable reduction of maternal complications but increased perinatal mortality. This decision was made after interdisciplinairy consultation and parent counselling. Studies on perinatal mortality and morbidity in these severely growth restricted premature infants do not support active neonatal management[14-16].

The accuracy of fetal weight estimation by ultrasound has been debated[17]. A recent study shows that determining the EFW in extreme preterm and SGA fetuses is less accurate than for AGA fetuses and that EFW is more likely to be overestimated[17]. Our study shows that in 22% of neonates the weight was more than 10% higher than estimated before birth. We recommend to take this inaccuracy into account when counselling parents with growth restricted fetuses at the limits of fetal viability.

Differences between centers:

We found considerable differences in prevalence of termination between centers. Because of the small numbers these differences should be interpreted with caution. It is possible that part of these differences may be explained by the socioeconomic differences of the adherent populations in the regions of these centers. Dutch studies show marked differences in maternal mortality and perinatal mortality between cities, provinces and neighbourhoods[18]. The Maternal Mortality Rate (MMR) in the four largest

cities in The Netherlands is significantly higher than the overall MMR in The Netherlands, with preeclampsia being the most frequent direct cause of death[20].

Some of the variation in prevalence may also be explained by different policies as to initiation of active neonatal support in infants born at the limits of viability between centers[21].

CONCLUSION

Termination of pregnancy for early-onset hypertensive disorders in fetuses considered non-viable, is extremely rare in The Netherlands. We identified on average 1 to 2 cases per year per tertiary obstetric care center. To reach the decision to terminate such pregnancies at the limits of fetal viability is very difficult for parents as well as health care providers. This is reflected in an average interval between admission and intervention of 9.3 days. However, considering the frequency of maternal complications termination of pregnancy and not expectant management should be considered for all women presenting with severe early onset hypertensive disorders at the limits of fetal viability. As neonatal intensive care continues to improve and enables survival at earlier gestational ages and lower birth weights it is prudent to continuously monitor the practice and outcomes to be able to define best-practices in the care of these complicated pregnancies.

REFERENCES

1. Lisonkova S, Joseph KS. Incidence of preeclampsia: risk factors and outcomes associated with early- versus late-onset disease. Am J Obstet Gynecol 2013;209:544.e1-12.
2. Zeeman GG. Neurologic complications of pre-eclampsia. Semin Perinatol 2009;33(3):166-72.
3. Gaugler-Senden IP, Huijssoon AG, Visser W et al. Maternal and perinatal outcome of preeclampsia with an onset before 24 weeks' gestation. Audit in a tertiary referral center. European J Obstet Gynecol 2006;128:216-221
4. Bombrys AE, Barton JR, Nowacki EA et al. Expectant management of severe preeclampsia at less than 27 weeks' gestation: maternal and perinatal outcome according to gestational age by weeks of onset of expectant management. Am J Obstet Gynecol 2008;199:247.el-247.e6
5. Sibai BM, Barton JR. Expectant management of severe preeclampsia remote from term: patient selection, treatment, and delivery indications. AM J Obstet Gynecol 2007;196:514.e1-9
6. NVOG modelprotocol LZA: Medisch handelen late zwangerschapsafbreking 2007. Available at http://nvog-documenten.nl/index.php
7. van Eerden L, Zeeman GG, Page-Christiaens GC et al. Termination of pregnancy for maternal indications at the limits of fetal viability: a retrospective cohort study in the Dutch tertiary care centres. BMJ open 2014 Jun 17;4 (6):e005145
8. NVOG Richtlijn Hypertensieve aandoeningen in de zwangerschap. 2011 Nederlandse Vereniging voor Obstetrie en Gynaecologie. Available at nvog-documenten.nl/index.php
9. The Netherlands Perinatal Registry. www.perinatreg.nl
10. Jenkins SM, Head BB, Hauth JC.. Severe preeclampsia at < 25 weeks of gestation: Maternal and neonatal outcomes. Am J Obstet Gynecol 2002;186:790-5
11. The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP. Tranquilli AL, Dekker G, Magee L, Roberts J, Sibai BM, Steyn W, Zeeman GG, Brown MA. Pregnancy Hypertens. 2014 Apr;4(2):97-104
12. NICE guideline Hypertension in Pregnancy August 2010. Available at: www.nice.org.uk/guidance/CG107
13. NVOG guideline Perinataal beleid bij extreme vroeggeboorte. Sept 2010. Available at: www.nvog.nl//Sites/Files/0000001346_Richtlijn%20Perinataal%20beleid%20bij%20extreme%20vroeggeboorte.pdf
14. Garite TJ, Clark R, Thorp JA. Intrauterine growth restriction increases morbidity and mortality among premature neonates. Am J Obstet Gynecol 2004;191:481e7.
15. Tsai LY, Chen YL, Tsou KI et al. The Impact of Small for Gestational Age on Neonatal Outcome among Very Low Birth Weight Infants, Pediatr Neonatol 2015 Apr;56(2):101-7.
16. Bernstein IM, Horbar JD, Badger GJ et al. Morbidity and mortality among very-low-birth-weight neonates with intrauterine growth restriction. The Vermont Oxford Network. Am J Obstet Gynecol 2000;182:198e206
17. Stefanelli S, Groom KM. The accuracy of ultrasound-estimated fetal weight in extremely preterm infants: a comparison of small for gestational age and appropriate for gestational age. Aus N Z J Obstet Gynaecol. 2014 ;54(2):126-31
18. Tromp M, Eskes M, Reitsma JB et al. Regional perinatal mortality differences in the Netherlands; care is the question. BMC Public Health 2009, 9:102
19. NVOG nota Verwijzing naar een perinatologisch centrum. Sept 2007. Available at: www.nvog-documenten.nl/index.php?pagina=/richtlijn/pagina.php&fSelectTG_62=75&fSelectedSub=62&fSelectedParent=75

20. de Graaf J, Schutte J, Poeran J et al. Regional differences in Dutch maternal mortality. BJOG 2012;119:582–588.
21. Rysavy MA, Li L, Bell EF et al. Between-Hospital Variation in Treatment and Outcomes in Extremely Preterm Infants. N Engl J Med 2015 May 7;372(19):1801-11

Chapter 4

Subsequent pregnancy outcome after mid trimester termination of pregnancy for preeclampsia

L van Eerden, CJM de Groot, GG Zeeman, GCM Page-Christiaens, E Pajkrt, JJ Duvekot, FP Vandenbussche, SG Oei, HCJ Scheepers, J van Eyck, JM Middeldorp, AC Bolte

Aust N Z J Obstet Gynaecol. 2018 Apr;58(2):204-209

ABSTRACT

Background

In this study we determined the outcome of subsequent pregnancies after termination of pregnancy for preeclampsia, with the purpose of presenting data useful for counseling these women on future pregnancies.

Study design

The cohort consists of 131 women with a history of termination of pregnancy for preeclampsia.

Results

Data of 79 pregnancies was available for analysis, including 13 women with chronic hypertension and 16 women with thrombophilia. There were 7 miscarriages (8.8%) and 72 ongoing pregnancies. Low dose aspirin was prescribed for 64 women (89%). The mean gestational age at delivery was $35^{6/7} \pm 4$ weeks with a mean birth weight of 2571 ± 938 grams. Overall recurrence rate for preeclampsia was 29% at a mean gestational age of 32 weeks. Thirty-eight women had an uncomplicated pregnancy (53%). The women with chronic hypertension had the highest recurrence rate of 38%. Neonatal mortality was 4%.

Conclusion

The course of subsequent pregnancies after mid trimester termination for preeclampsia is uncomplicated in 53% with a recurrence rate for preeclampsia of 29%. The mean gestational age at delivery was 11 weeks later and birth weight 2000 grams higher than in the index pregnancy.

INTRODUCTION

Preeclampsia is a multi-systemic disorder clinically characterized by new onset or worsening of chronic hypertension and presence of either proteinuria or end organ dysfunction or both after 20 weeks' gestation[1]. Clinical risk factors for developing preeclampsia include: nulliparity, a history of preeclampsia, pre-existing conditions such as chronic hypertension and renal disease, advanced maternal age and the presence of antiphospholipid antibodies[2,3]. The prevalence of preeclampsia is estimated at 3-5% of all pregnancies worldwide[4]. In rare instances preeclampsia occurs whilst the fetus is not considered viable. Previous publications have contributed to the option of termination of pregnancy (TOP) in these cases to prevent severe maternal morbidity and mortality[5,6].

Recently, we published our nationwide retrospective cohort study in The Netherlands in which we reviewed all terminations of pregnancy for preeclampsia[7]. In the current project we determined the outcome of subsequent pregnancies, with the purpose of collecting data useful when counseling women with a history of termination of pregnancy for preeclampsia.

MATERIALS AND METHODS

This retrospective cohort study included women who underwent termination of pregnancy for preeclampsia in The Netherlands between 2000-2009. Under Dutch legislation termination of pregnancy (TOP) is possible up to the gestational age where a newborn can survive outside the womb. This is currently considered $24^{0/7}$ weeks for adequately grown fetuses without lethal disorders and a sufficient amount of amniotic fluid for lung development[8]. Up to 2010 termination of pregnancy beyond 24 weeks' gestation for life- threatening maternal conditions in combination with dismal fetal prospects did not have to be reported to the District Attorney, since termination of pregnancy in such cases is considered inevitable to prevent deteriorating maternal morbidity or even mortality. Between 2000 and 2009 national guidelines concerning active neonatal support were in place. Prior to 2006 the limit for active obstetric and neonatal management was 26 weeks' of gestation. After 2006 the recommended limit was 25 weeks' gestation, with an estimated fetal weight of at least 500 grams.

Termination of pregnancy was defined as termination of a vital pregnancy and intention of primary non-intervention for fetal indications. In all cases the fetus was considered to be non-viable, because of the periviable gestational age with concomitant severe growth restriction[9].

Exclusion criteria for this study were termination of pregnancy for other maternal indications, fetal congenital anomalies or intra-uterine fetal demise prior to the decision

to termination of pregnancy. The decision to terminate the pregnancy was made after counseling by a multidisciplinary team, consisting of at least obstetricians and neonatologists. In all cases it was a shared decision with the parents. All terminations were performed in one of the ten tertiary perinatal care centers in The Netherlands, using prostaglandins (i.e. intravenous sulprostone or misoprostol)[10]. We collected outcome data of the first subsequent pregnancy after the index pregnancy. The last patient was included in January 2015. All charts were reviewed by the first or the last author and extracted data were recorded on a standardized form. The following data were registered: recurrent preeclampsia and gestational age at recurrence, gestational hypertension, gestational age at delivery and use of low-dose aspirin as well as additional maternal risk factors as chronic hypertension and thrombophilia. Neonatal outcome data recorded were: gender, birth weight, birth weight centile and perinatal mortality. Small for gestational age (SGA) was defined as a birth weight below the 10th percentile. During the study period of the index pregnancies screening for thrombophilia was advised in the context of an international clinical trial[11]. The tests performed included: protein S deficiency, protein C deficiency, antithrombin deficiency, factor V Leiden mutation, prothrombin mutation, lupus anticoagulant, anticardiolipin antibodies and hyperhomocysteinemia.

Preeclampsia and gestational hypertension were defined according to the definitions of the International Society for the Study of Hypertension in Pregnancy (ISSHP)[1]. Chronic hypertension was defined as hypertension with antihypertensive drugs prior to pregnancy or indication to start antihypertensive drugs prior to 20 weeks' gestation. Early preeclampsia was defined as the occurrence of preeclampsia and indicated delivery prior to a gestational age of 32 weeks.

Statistical analysis was performed using SPSS 20.0 (SPSS Inc.,Chicago, Il, USA). Continuous variables were expressed as means with standard deviations (SD). Differences between the groups were tested with an unpaired t-test or a χ-square test as appropriate. P value less than 0.05 was considered to indicate statistical significance.

The ethical advisory board of the VU Medical Centre evaluated the study and decided that this study to be exempt from formal ethical review (VUmc # 29-2010/200)

POPULATION

The cohort of index pregnancies consisted of 131 women who underwent termination of pregnancy because of severe maternal hypertensive disorders between 22 and $27^{6/7}$ weeks of pregnancy. Table 1 shows the maternal characteristics during the index pregnancy.

	Mean (SD) or N (%)
Age	30.4 ± 5.2 years
Parity	
Nulliparous (no pregnancies GA > 16 weeks)	69 (81%)
Multiparous	16 (19%)
Live offspring	13 (81%)
Previous perinatal death	4 (25%)
Previous PE or HELLP	4 (25%)
Medical history	
No known pre-existing conditions	61 (72%)
Chronic hypertension	15 (18%)
Thrombophilia	5 (5.9%)
Other*	4 (4.7%)
Maternal outcome	
HELLP syndrome	53 (62%)
Eclampsia	5 (5.9%)
ICU admission**	8 (9.4%)

Table 1. Maternal characteristics in the index pregnancy
* Other: Diabetes Mellitus, obesity, SLE, Crohn's disease, osteosarcoma
** Admission to ICU included women with pulmonary edema, refractory hypertension, eclampsia, heart failure and hypovolemic shock

The decision to offer termination of pregnancy was made after interdisciplinary consultation with the neonatologist and was guided by poor fetal prognosis, where chances for intact neonatal survival were assumed non-existent. The mean gestational age at termination was $24^{5/7}$ ±1,5 weeks with a mean birth weight of 469 ± 124 grams. Eighty women (61%) developed HELLP syndrome in the index pregnancy[7].

RESULTS

Of the 103 women with a history termination of pregnancy for preeclampsia and follow up, 85 women (83%) had at least one subsequent pregnancy (Figure 1).

Of these women 71 had no living children (84%). Eighteen women did not conceive again of whom ten (56%) had already one or more living children. Data from 79 pregnancies was available for analysis, including 67 singleton pregnancies, 4 twin pregnancies and 1 triplet. Seven women (8,8%) had a first trimester miscarriage.

Of 72 ongoing pregnancies the mean gestational age at delivery was $35^{6/7}$ ± 4 weeks with a mean birth weight of 2571 ± 938 grams (table 2).

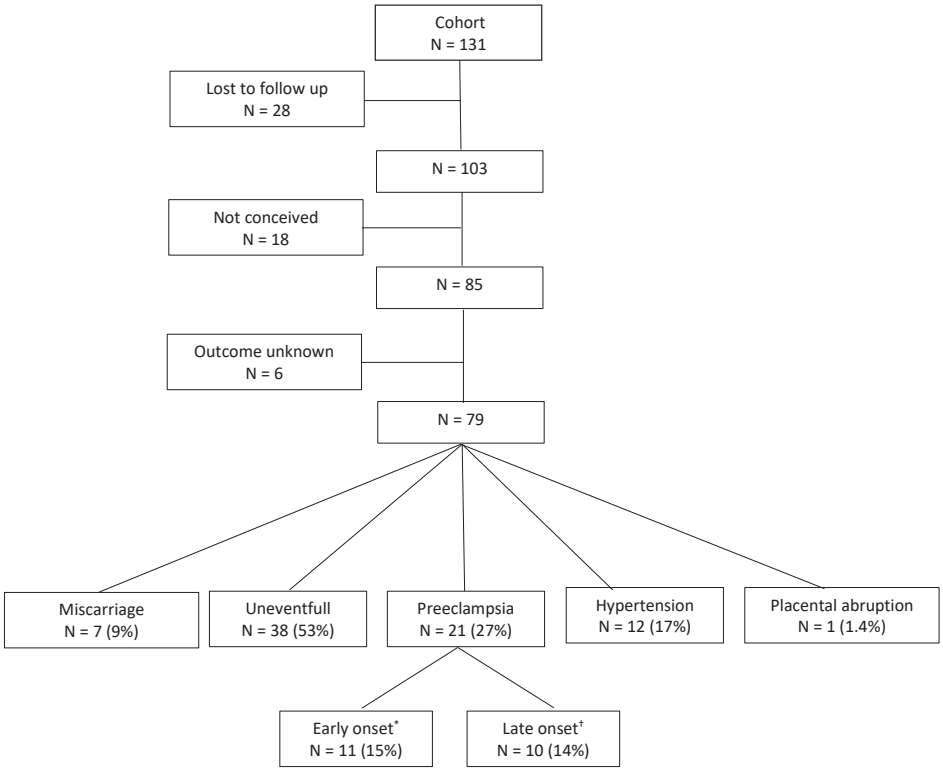


Figure 1. Figure 1: Flow chart Pregnancy outcome in the cohort.
* = delivery prior to 32 weeks' gestation
† = delivery after 32 weeks' gestation

Ongoing pregnancy (N =72)	**Mean (SD) or N (%)**
Gestational age at delivery	$35^{6/7} \pm 4$ weeks
Uncomplicated	38 (53%)
PE overall	21 (29%)
HELLP	2 (2.7%)
PE delivery < GA 32 weeks	11 (15%)
Birth weight overall *	2571 ± 938
Birth weight singletons *	2567 ± 965
IUGR†	9 (13%)
Neonatal mortality	3 (4%)
Outcome with recurrent PE	N = 21
GA delivery (weeks ± SD)	$32^{0/7} \pm 4$ weeks
Birth weight (grams ± SD)	1562 ± 984
PE with low dose aspirin	15/64 (23%)
PE no aspirin	6/8 (75%)

Table 2. Pregnancy outcome after mid trimester termination for preeclampsia
* Birth weight is provided in grams
† IUGR is birth weight below the 10th percentile using the Dutch reference charts[21]

The recurrence rate of preeclampsia was 29% (21/72), and the recurrence rate of early onset preeclampsia was 15% (11/72). The mean gestational age at delivery with recurrent preeclampsia was $32^{0/7} \pm 4$ weeks and the mean birth weight was 1562 ± 984 grams. All multiple pregnancies were delivered after 32 weeks' gestation. In one twin pregnancy preeclampsia reoccurred.

Eighty-nine % (64/72) of women with an ongoing pregnancy received low dose aspirin (80 mg daily started before 12 weeks gestation), seven of the women also received low molecular weight heparin (LMWH). Of the eight women not receiving low dose aspirin, six developed preeclampsia (75%) compared to 15/64 women who did receive low dose aspirin (23%).

Table 3 shows the pregnancy outcome in women with chronic hypertension.

	CHTN† N = 13 (%)	**normotensive N = 59 (%)**	**Significant p<0.05***
GA delivery (weeks)	$33^{2/7} \pm 4$	$36^{2/7} \pm 4$	p = 0.017#
PE	5 (38%)	16 (27%)	p = 0.415
PE < 32 weeks**	4 (31%)	7 (12%)	p = 0.086
Birth weight (grams)	2161 ± 901	2680 ± 937	p = 0.081
IUGR***	4 (30%)	5 (8%)	p = 0.073

Table 3. Pregnancy outcome in women with chronic hypertension and women without chronic hypertension

† CHTN = chronic hypertension

indication of statistical difference

* group differences were tested using the unpaired t-test or χ-square test, with a p<0.05 indicating significance

** PE with delivery < 32 weeks' gestation

***IUGR is birth weight below the 10th percentile using the Dutch reference charts[22]

The recurrence rate of preeclampsia for women with chronic hypertension was 38% (5/13). The mean gestational age at delivery in these women was $33^{2/7} \pm 4$ weeks and is significantly lower compared to normotensive women. The mean birth weight was 2161 ± 901 grams. Outcome of subsequent pregnancies in 59 women without chronic hypertension shows a mean gestational age at delivery of $36^{2/7} \pm 4$ weeks with a mean birth weight of 2680 ± 937 grams.

Results of thrombophilia screening were available for 97 women (74%). Thrombophilia screening was offered in context of an ongoing study[11]. In 71% (69/97) test results were negative. In 29% (28/97) there were positive test results: 11% had antiphospholipid antibodies, 9% had hyperhomocysteinemia and 8% were found to have hereditary thrombophilia. Twenty women conceived again, of which 2 women miscarried. Two women were lost to follow up. Low dose aspirin prophylaxis was prescribed in the 16 women with an ongoing pregnancy. Six of them also received heparin (LMWH). The women with

hyperhomocysteinemia were all treated with vitamin B supplements. The recurrence rate of preeclampsia was 31% (5/16), of which 3 women delivered prior to 32 weeks. The mean gestational age at delivery was $35^{5/7} \pm 4$ weeks with a mean birth weight of 2500 ± 915 grams. In the women without thrombophilia the recurrence rate for preeclampsia was 27% (12/45). The mean gestational age was $36^{0/7} \pm 4$ weeks and the mean birth weight was 2655 gram ± 944 grams. There were no statistically significant differences in recurrence rate of preeclampsia between women with or without thrombophilia.

The neonatal mortality was 4% (3/72) (table 1). Two of the pregnancies were complicated by early onset preeclampsia with gestational ages 25 weeks and $26^{3/7}$ and birth weight p15 and p20 respectively. Both neonates, delivered via cesarean section, did not survive due to complications of prematurity. The third pregnancy was complicated by a placental abruption. This male neonate was delivered by an emergency Caesarean section at $28^{2/7}$ weeks' gestation and weighed 1100 grams (p20).

Eleven percent of neonates (9/78) were small for gestational age of which 5 neonates had a birth weight below the 2,3th percentile. Women who developed superimposed preeclampsia all delivered neonates with a birth weight appropriate for gestational age. In the women with thrombophilia 5 neonates were small for gestational age (26%).

COMMENT

Main findings

In rare instances termination of pregnancy is performed for maternal hypertensive disorders. Studies describing recurrence rates and outcome in subsequent pregnancies for this specific group are very limited. This retrospective study presents data on the first subsequent pregnancy. In 53% the course of subsequent pregnancy was uneventful. The recurrence rate for preeclampsia was 29% at a mean gestational age of 32 weeks. However, in those with recurrent preeclampsia, the mean gestational age was 8 weeks later and the birth weight was more than 1000 grams higher than in the index pregnancy. Overall neonatal survival rate was 96%.

Women with chronic hypertension (CH) delivered on average 3 weeks earlier than normotensive women with a history of termination of pregnancy for preeclampsia. The recurrence rate of early onset PE was 31% versus 10% in women with and without chronic hypertension.

The women with thrombophilia were all treated with either low dose aspirin or a combination of low dose aspirin and LMWH and vitamin B supplements as appropriate and had similar pregnancy outcomes compared to the women without thrombophilia.

Strengths and weaknesses

The strength of this study is that it describes a rather large, national cohort considering the rareness of extremely early onset preeclampsia. During the study period national guidelines for management of pre-eclampsia and postdelivery diagnostic protocols for underlying diseases remained unchanged[10,11]. Furthermore, detailed medical history and outcome information were available, since data was gathered from the medical records.

The retrospective nature of this study is its main limitation. Even though a major effort was put in obtaining information on subsequent pregnancies, 21% of the women of the original cohort were lost to follow up. The sample size in the subgroups is too small to show a statistically significant difference in recurrence of preeclampsia between the groups. Therefore, a more detailed assessment of factors predictive of recurrent pre-eclampsia cannot be provided. The sample size also prohibits generalizability to other populations. Another limitation is missing information about the interval between the index pregnancy and subsequent pregnancies and whether or not the woman conceived with the same partner. Furthermore there is no data available on neonatal morbidity.

Interpretation

The overall recurrence rate of preeclampsia in our study is 29%. Other studies showed variable recurrence rates of preeclampsia of 14%-55%[12-15]. Recurrent early onset pre-eclampsia, resulting in a delivery before 32 weeks' gestation, occurred in 15% of cases in our study, compared to 5%-44%[12-14]. Comparable to the literature (33%)[16] women with chronic hypertension had the highest recurrence rate of early onset preeclampsia of 31% versus 10% in women without chronic hypertension. Even though this is not a statistically significant difference, likely due to a small sample size, it may be clinically relevant and should be taken into account when counseling women on future pregnancies.

In our cohort the incidence of HELLP syndrome in the index pregnancy was high (62%). A study by Chames and co-workers explicitly looked at the recurrence of pre-eclampsia after HELLP syndrome in a previous pregnancy prior to 28 weeks' gestation[12]. They report a recurrence rate of 55%, which is much higher than what we found in our study (29%). In the aforementioned study the women with chronic hypertension also had the highest recurrence risk. The study does not describe any other risk factors for preeclampsia besides chronic hypertension, nor is there information about the use of low dose aspirin. Another Dutch study found a recurrence rate of 50%. The risk of recurrence was significantly increased in women with chronic hypertension. This is comparable to our results[13].

Eighteen women did not conceive again in our cohort (17%). In a study by Langeveld and coworkers 32% of women with a hypertensive disorder resulting in a delivery prior

to 34 weeks' gestation, did not conceive again. Of this group 64% refrained from a next pregnancy because of fear of recurrence[16]. The lower percentage of women in our group can possibly be explained by the fact that the perinatal death rate in the index pregnancies was 100%, leaving many of the women childless. Furthermore, in the past years more data has become available on recurrence and survival in a next pregnancy following a pregnancy with a hypertensive disorder. Probably, this is currently taken into account when counseling these women on future pregnancies.

Screening for thrombophilia was positive in 29% of the women. Other studies found incidences varying from 24-51% for inherited thrombophilia[14,17,18] and up to 16% for antiphospholipid syndrome[19]. Screening for thrombophilia in a high risk population remains controversial. Screening for inherited thrombophilia in women with early onset preeclampsia is not recommended in the latest practice bulletin by the American College of Obstetricians and Gynecologists nor by the Dutch guideline, because there is insufficient evidence to conclude that inherited thrombophilia is associated with preeclampsia[20,21]. Systematic reviews have reported a significant association between anticardiolipin antibodies or lupus anticoagulant and development of severe preterm preeclampsia[19]. In our study 74% of the women were screened for thrombophilia. These tests were performed in the context of a clinical trial. In current practice routine screening for thrombophilia after early-onset preeclampsia is no longer performed, because prevention with low dose aspirin is advised regardless of the presence or absence of antiphospholipid antibodies. There is sufficient evidence showing that the use of low dose aspirin, started before 16 weeks' gestation reduces the risk of preeclampsia especially in women at high risk[23-25]. Therefore the World Health Organization as well as the American College of Obstetricians and Gynecologists and the National Institute for Health and Care Excellence (NICE) advise low dose aspirin for the prevention of preeclampsia in high risk women[26-28]. However in our cohort not all women were treated according to this advice, for reasons that did not become apparent from the medical records. Of the women in our cohort who were and were not treated with low dose aspirin in the subsequent pregnancy, 23% and 75% respectively developed preeclampsia again, supporting the advice to prescribe low dose aspirin to these high risk women.

CONCLUSION

Maternal and neonatal outcome in a subsequent pregnancy after a previous termination of pregnancy for preeclampsia is generally favorable. In 53% the pregnancy was uneventful and most women did not develop recurrent preeclampsia. The overall recurrence rate is 29% at a mean gestational age of 32 weeks. Women with chronic hypertension have the highest recurrence risk. The perinatal mortality is low (4%). Furthermore,

the mean gestational age at delivery is more than 11 weeks later and the neonatal birth weight is more than 2000 grams higher. Prescription of low dose aspirin is advised. These data might be useful in counseling women with a history of termination of pregnancy for preeclampsia.

REFERENCES

1. The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP. Pregnancy Hypertension 4 (2014): 97-104
2. Milne F, Redman C, Walker J et al. The pre-eclampsia community guideline (PRECOG): how to screen for and detect onset of pre-eclampsia in the community. BMJ. 2005;330(7491):576.
3. Caughey AB, Stotland NE, Washington AE et al. Maternal ethnicity, paternal ethnicity and parental ethnic discordance: risk factors of preeclampsia. Obstet Gynecol. 2005;106(1):156.
4. Abalos E, Cuesta C, Grosso AL et al. Global and regional estimates of preeclampsia and eclampsia: a systematic review. Eur J Obstet Gynecol Reprod Biol. 2013 Sep;170(1):1-7.
5. NICE guideline Hypertension in Pregnancy August 2010. Available at: www.nice.org.uk/guidance/CG107
6. Sibai BM, Barton JR. Expectant management of severe preeclampsia remote from term: patient selection, treatment, and delivery indications. AM J Obstet Gynecol 2007;196:514.e1-9
7. van Eerden L, van Oostwaard MF, Zeeman GG et al. Terminating pregnancy for severe hypertension when the fetus is considered non-viable: a retrospective cohort study. Eur J Obstet Gynecol Reprod Biol 206 (2016) 22–26
8. www.wetboek-online.nl//wet/Sr/82a.htlm
9. van Eerden L, Zeeman GG, Page-Christiaens, GCM, et al. Termination of pregnancy for maternal indications at the limits of fetal viability: a retrospective cohort study in the Dutch tertiary care centres. BMJ Open 2014;4:e005145. doi:10.1136/bmjopen-2014-005145
10. NVOG Nota Verwijzing naar een perinatologisch centrum. 2007 Nederlandse Vereniging voor Obstetrie en Gynaecologie. Available at http://nvog-documenten.nl/index.php
11. de Vries JIP, van Pampus MG, Hague WM et al. Low-molecularweight heparin added to aspirin in the prevention of recurrent early-onset pre-eclampsia in women with inheritable thrombophilia: the FRUIT-RCT. J Thromb Haemost 2012; 10: 64–72
12. Chames MC, Haddad B, Barton JR et al. Subsequent pregnancy outcome in women with a history of HELLP syndrome at ≤ 28 weeks of gestation. Am J Obstet Gynecol 2003; Volume 188 (6):1504-7; discussion 1507-8.
13. Gaugler-Senden IMP, Berends AL, de Groot CJM et al. Severe, very early onset preeclampsia: Subsequent pregnancies and future parental cardiovascular health. Eur J Obstet Gynecol Reprod Biol 140 (2008) 171–177
14. van Rijn BB, Hoeks LB, Bots ML et al. Outcomes of subsequent pregnancy after first pregnancy with early-onset preeclampsia. Am J Obstet Gynecol 2006; 195, 723–8
15. Mostello D, Kallogjeri D, Tungsiripat R et al. Recurrence of preeclampsia: effects of gestational age at delivery of the first pregnancy, body mass index, paternity, and interval between births. Am J Obstet Gynecol 2008;199:55.e1-55.e7.
16. Langenveld J, Buttinger A, van der Post J et al. Recurrence risk and prediction of a delivery under 34 weeks of gestation after a history of a severe hypertensive disorder. BJOG 2011;118:589–595.
17. Miyakis S, Lockshin MD, Atsumi T et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006; 4: 295–306.
18. Sibai, BM. Thrombophilia and severe preeclampsia: time to screen and treat in future pregnancies? Hypertension 2005;46:1252-3.

19. do Prado AD, Piovesan DM, Staub HL et al. Association of anticardiolipin antibodies with pre-eclampsia. A systematic review and meta-analysis. Obstet and Gynecol; vol 116, no. 6, December 2010
20. The American College of Obstetricians and Gynecologists. Practice bulletin: Inherited Thrombophilias in pregnancy. Obstet and Gynecol vol 122, no.3, September 2013
21. Antitrombotisch beleid. www.richtlijnendatabase.nl p193-196
22. www.perined.nl/producten/geboortegewichtcurven
23. Henderson JT, Whitlock EP, O'Connor E et al. Low-Dose Aspirin for the Prevention of Morbidity and Mortality From Preeclampsia: A Systematic Evidence Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 112.AHRQ Publication No. 14-05207-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2014.
24. Coomarasamy A, Honest H, Papaioannou S et al. Aspirin for prevention of preeclampsia in women with historical risk factors: a systematic review. Obstet Gynecol. 2003 Jun;101(6):1319-32
25. Roberge S1, Villa P, Nicolaides K et al. Early administration of low-dose aspirin for the prevention of preterm and term preeclampsia: a systematic review and meta-analysis. Fetal Diagn Ther. 2012;31(3):141-6
26. WHO recommendations for Prevention and treatment of pre-eclampsia and eclampsia. World Health Organization 2011.
27. American College of Obstetricians and Gynecologists. Hypertension in Pregnancy-Practice Guideline 2013.
28. NICE Quality Standard Hypertension in Pregnancy. 2013

Chapter 5

Induction of labor for maternal indications at a periviable gestational age; survey on management, reporting and auditing amongst Dutch Maternal-Fetal Medicine Specialists and Neonatologists

L van Eerden, CJM de Groot, GCML Page-Christiaens,
E Pajkrt, GG Zeeman and AC Bolte

Accepted Am J Perinat Reports

ABSTRACT

Background

In cases of life-threatening maternal conditions in the periviable period, professionals may consider immediate delivery, with fetal demise as a consequence of the treatment. We sought the opinion of involved medical professionals on management, reporting and auditing in these cases.

Methods

We performed an online survey amongst all registered maternal-fetal medicine specialists (MFM specialists) and neonatologists in The Netherlands. The survey presented 2 hypothetical cases of severe early-onset pre-eclampsia at periviable gestational ages. Management consisted of immediate termination or expectant management directed towards newborn survival.

Findings

In the case managed by immediate termination, 62% percent answered that fetal demise resulting from induction of labor for maternal indications should be audited only within the medical profession. In the case of expectant management, 17% of the participants agreed with this management. Some answers revealed a significant difference in opinion between the medical specialists.

Conclusion

Perspective of MFM specialists and neonatologists differs with regard to counseling prospect parents in case of severe early onset preeclampsia. The majority of professionals is willing to report late termination (after 24 weeks' gestation) for severe maternal disease to medical experts for internal audits, but not for legal auditing.

BACKGROUND

Dutch legislation on termination of pregnancy has been in place since 1981 and regulations on termination of pregnancy after 24 weeks' gestation, the so called 'late terminations', since 2007. In 2016 Dutch regulations for late termination of pregnancy have been revised by the Ministries of Justice and Health in order to promote reporting and auditing. This was preceded by a formal evaluation of the existing regulations and a debate amongst professionals. The current study was done in the framework of this debate.

In the Netherlands termination of pregnancy is, subject to a number conditions such as parental request and reflection time, exempted from legal prosecution up to the moment where the newborn is judged to be viable outside the womb. This is usually considered to be after $24^{0/7}$ weeks of gestation for adequately grown fetuses with a sufficient amount of amniotic fluid for lung development and without life threatening congenital disorders[1].

Termination for nonmedical reasons is usually performed in licensed abortion clinics up to 22 weeks. Terminations for genetic reasons or medical maternal disorders are performed in obstetric units of secondary or tertiary care hospitals. In the Netherlands approximately 30000 pregnancies are terminated up to 24 weeks on an annual base. Half of these take place before 7 weeks' gestation and 3 percent after 21 weeks. Twelve percent of women undergoing termination of pregnancy are not residing in The Netherlands. There is an annual report of the Health Care Inspectorate in an aggregated form[2].

In case of termination beyond 24 weeks the procedure is the following: every death of a minor, including induced or spontaneous stillbirth after $24^{0/7}$ weeks has to be reported to the Municipal Coroner, who then reports to the District Attorney[3]. This also accounts for neonatal deaths on neonatal care units as well as fetal demise during labor and delivery. Up to early 2016 the cases of termination were further subject to review by one of two expert committees[4]. In case of lethal fetal disorders, the so-called category 1, a committee of the Dutch Society of Obstetrics and Gynecology performed an internal audit and reported anonymous and aggregated to the member gynecologists as well as to the Dutch Health Care Inspectorate. Category 2 pertained to cases with severe, but not necessarily lethal disorders where neonatologists would refrain from senseless postnatal intervention. Cases in this category were audited by a committee appointed by the Ministries of Justice and Health[4] and reported on a case by case basis to the Attorney General, the highest legal authority in The Netherlands. As from early 2016 both committees have been merged. The current committee consists of four medical specialists, one lawyer and one ethicist[5].

Induction of labor for maternal indications at a periviable gestational age was noted in the former regulation but not extensively addressed. In the new regulation cases of

induction of labor for maternal indications do not have to be reported to the aforementioned committee. Annually, there are about 25 terminations of pregnancy for maternal indications in the Netherlands[6]. Approximately 12 of these take place at or shortly after 24 weeks. Up to now these cases were rarely reported to the District Attorney, because fetal demise was considered the inevitable consequence of the treatment of the mother, and because of lack of clear guidelines. With our survey we aimed to help clarify the issues at stake. Also the results of this survey can be used to reopen the discussion amongst professionals and gain uniformity of registration and auditing in a newly to be developed registration system after introduction of the new regulations.

DESIGN AND METHODS

Survey design

All registered Maternal-Fetal Medicine (MFM) specialists and neonatologists in The Netherlands were invited to participate in an online survey, using a commercial internet-based service (surveymonkey.com®). Both disciplines are involved as well in patient counselling as in the evaluation of the regulations. We approached both disciplines separately. The survey invitation included a cover letter stating the study's objective, the voluntary and anonymous nature of the study, the intent to use the data in a publication, and contact information. By completing the survey the participants consented to these terms. The ethical advisory board of the VU Medical Centre evaluated the survey and exempted the study from formal ethical review (VUmc # 29-2010/200)[7].

The survey presented 2 hypothetical cases of severe preeclampsia in combination with dismal fetal prospects based on historical patient records. The cases are summarized in Figure 1 and 2.

The survey questions were pretested by 8 reviewers who were representative for the study-population. The reviewers assessed clarity and content, order of questions and total time needed to complete the survey. The final survey consisted of seven multiple answer questions. The four questions accompanying the first case were on reporting and auditing and the three questions accompanying the second case were on management. It took approximately ten minutes to complete the survey.

Survey distribution

An invitation with a link to the survey was sent by e-mail to all MFM specialists (n=197) and neonatologists (n= 282) registered in the Netherlands either as a member of either the Dutch Society of Obstetrics and Gynecology or the Paediatric Association of The Netherlands in 2015. Two months after the initial approach we sent a reminder. Four months after the first invitation, the survey was closed.

Case 1:

A 20 year old primigravid woman is admitted to the hospital with preeclampsia at a gestational age of $24^{2/7}$ weeks. She is treated with antihypertensive medication and magnesiumsulphate to prevent eclampsia. Fetal ultrasound shows signs of severe growth restriction (EFW 359 grams) and an abnormal flow profile in the umbilical artery. At a gestational age of 25 weeks her condition deteriorates and the decision is made to terminate the pregnancy in order to prevent worse maternal outcome. Because of the severe fetal growth restriction labor is induced with prostaglandins. No fetal monitoring is performed. She delivers a still born son with a birth weight of 412 grams. She makes a full recovery within one week.

Questions*

- Do you think this case should have been reported to the municipal coroner?
- Do you think such cases should be audited by either the professional society or by the district Attorney or by both or by neither?
- Are you willing to report such cases to the committee of The Dutch Society of Obstetrics and Gynecologists for an internal audit?
- Do you think such cases should be reported to an expert committee

Figure 1. Case 1. * = possible answers consist of yes, no or I don't know and a free text option

Data management

Results are presented as absolute numbers and percentages. Statistical analysis was performed with SPSS 20.0 (SPSS Inc., Chicago, IL, USA). Differences were tested with a Fisher's exact test as appropriate. P values less than 0.05 were considered statistically significant.

RESULTS

The overall response rate was 37% (175), 34% amongst the MFM specialists (n=66) and 39% amongst the neonatologists (n=109).

Answers to questions on case 1 are shown in table 1 and 2. In this case labor was induced for severe early-onset preeclampsia after a gestational age of 24 weeks with an EFW of 359 grams. Fetal demise was not reported to the Municipal Coroner

Case 2

A 28 year old primigravid woman is admitted to the intensive care unit with preeclampsia at a gestational age of $23^{2/7}$ weeks. She is treated with magnesiumsulphate to prevent eclampsia. To control her blood pressure three different types of antihypertensives are needed. The pregnancy is managed expectantly in order to reach a term where the fetus is considered viable. During this period of expectant management she suffers from two different episodes with eclamptic seizures.

At 25 weeks' gestation a caesarean section is performed. She delivers a baby girl with a birth weight of 495 grams ($< 2.3^{th}$ percentile). The girl is admitted to the neonatal intensive care unit. After three days she dies from complications related to prematurity.

The mother has still problems with concentration and has a mild afasia.

Questions*

- Do you agree with the chosen management to prolong the pregnancy to reach a viable term for the foetus?
- Do you think a pregnancy should be terminated immediately after an eclamptic seizure?
- In this case would you have performed a caesarean section before GA of 25 weeks?

Figure 2. Case 2. * = possible answers consist of yes, no or I don't know and a free text option

Sixty-two percent of the participants believed that fetal demise as a result of induction of labor for maternal indications should be subject to auditing within the medical profession only and that it should never be subject to legal audit (table 1).

Profession	Peers only (%)	Legal only (%)	Both (%)	None (%)
MFM specialists	42 (67)*	-	11 (17)*	10 (16)*
Neonatologists	59 (60)*	3 (3)*	14 (14)*	23 (23)*
Total	101 (62)	3 (2)	25 (15)	34 (21)

Table 1. (case 1): Question: do you think these cases should be subject to audits? If yes, what kind of audit, within the medical profession, legal audits, both or none?
Numbers are presented as absolute numbers according to profession
* percentages are shown as percentages within the profession

Fifty percent of the respondents argued that this case should have been reported to the Municipal Coroner. Furthermore seventy-three percent of all participants would be willing to report cases of termination for maternal indications resulting in fetal demise to the an expert committee of the Dutch Society of Obstetrics and Gynecology. Thirty-three percent of all participants would be willing to report these cases to an expert committee appointed by the Ministries of Health and Justice, advising the Attorney General whether or not to prosecute the MFM-specialist (table 2).

Profession	Yes (%)	No (%)	Unknown (%)	p
Question: Do you think this case should have been reported to the municipal coroner?				
MFM-specialist	44 (70)*	19 (30)*	-	
Neonatologist	37 (37)*	49 (49)*	13 (13)*	
Total	81 (50)	68 (42)	13 (8)	0.0015
Would you be willing to report this case to an expert committee of the Dutch Society of Obstetrics and Gynecology for an internal audit?				
MFM-specialist	51 (85)*	9 (15)*		
Neonatologist	63 (66)*	24 (25)*	9 (9)*	
Total	114 (73)	33 (21)	9 (6)	0.1067
Do you think such cases should be reported to an expert committee appointed by the Ministries of Health and Justice?				
MFM-specialist	18 (30)*	35 (58)*	7 (12)*	
Neonatologist	32 (33)*	42 (44)*	22 (23)*	
Total	51 (33)	77 (49)	29 (18)	0.3579

Table 2. Answers to the questions on case 1.
Numbers are presented as absolute numbers (percentages) according to profession
* percentages are shown as percentages within the profession

Fourteen percent (n=22) of participants recorded specific reasons in the free text box for their hesitation to report induction of labor for severe early-onset preeclampsia at a periviable gestational age to the expert committee appointed by the Ministries of Justice and Health. The given answers were: there are no other treatment options for the mother besides immediate delivery (n=9) and fear of legal judgment could delay appropriate care (n=4). Six respondents felt that a multidisciplinary consultation and consensus between the involved medical specialties prior to the decision to induce labor, should be sufficient. Three participants feared legal prosecution.

Answers to questions on case 2 are shown in table 3. In this case the patient developed severe early onset preeclampsia at a gestational age of $23^{2/7}$ weeks. During expectant management she suffered multiple eclamptic seizures. At a gestational age of 25 weeks a caesarean section was performed. The mother has residual symptoms, the baby girl did not survive (figure 2).

Profession	Yes (%)	No (%)	No answer (%)	p
Question: Do you agree with the chosen management to prolong the pregnancy to reach a viable term for the fetus?				
MFM specialists	5 (8)*	50 (82)*	6 (10)*	
Neonatologists	21 (22)*	49 (52)*	25 (26)*	
Total	26 (17)	99 (63)	31 (20)	0.0042
Question: Do you think a pregnancy should be terminated immediately after an eclamptic seizure?				
MFM specialists	42 (75)*	12 (21)*	2 (4)*	
Neonatologists	36 (38)*	16 (17)*	43 (45)*	
Total	78 (52)	28 (18)	45 (30)	0.3808
Question: In this case would you have performed a caesarean section before GA of 25 weeks?				
MFM specialists	13 (23)*	38 (68)*	5 (9)*	
Neonatologists	37 (39)*	33 (35)*	25 (26)*	
Total	50 (33)	71 (47)	30 (20)	0.0029

Table 3. Answers to the questions on case 2.
Numbers are presented as absolute numbers according to profession
* percentages are shown as percentages within the profession

Only seventeen percent of the participants agreed with the chosen expectant management and most of these were neonatologists (table 3).

Seventy-five percent of MFM specialist answered that an eclamptic seizure is always a reason to terminate the pregnancy. Thirty-three percent of participants stated that they would have delivered via caesarean section even prior to 25 weeks. Neonatologists were more in favor of a caesarean section than MFM specialists.

At the end of the survey there was a free text box for recommendations and remarks. Twenty-one neonatologists (19%) mentioned that the parents' wishes should be leading in the choice between induction of labor versus active management. Eighteen (27%) MFM-specialists gave a remark of which thirteen (20%) stated that the maternal condition should be leading in the choice between immediate delivery versus expectant management. Only five MFM specialists shared the opinion with the neonatologists that the parents' wishes should be leading (8%).

DISCUSSION

As part of an active debate on the procedures to be followed in case of late termination of pregnancy for maternal indications, this study interrogated the opinion of MFM specialists and neonatologists on management, reporting and auditing of two exemplary cases. In general immediate delivery is considered to be the only effective treatment for the mother in cases of severe maternal illness such as severe early-onset pre-eclampsia[8].

Our survey indicates that the majority of Dutch MFM specialists and neonatologists agree to report late termination of pregnancy for maternal indications to a committee of medical experts for auditing purposes, but not to the District Attorney who may recommend legal prosecution. This opinion is based on the thought that fear for legal prosecution could lead to postponing induction of labor, the only effective treatment, in this way putting the mother at an unacceptable risk for severe morbidity and mortality[8]. In the Netherlands preeclampsia is still the leading cause of direct maternal mortality and twice as frequent as thromboembolism. In the United Kingdom the reverse is true[9,10].

We presented two cases to all Dutch MFM specialists and neonatologists. The first case presented a preeclamptic women whose fetus was severely growth-restricted, the estimated fetal weight being 359 grams. Termination of pregnancy was judged necessary because of the maternal situation. No fetal monitoring was performed, nor was there willingness to perform a caesarean section or active neonatal resuscitation. Caesarean sections at an extreme premature gestational age are associated with a high risk of maternal morbidity (23% after caesarean delivery versus 3.5% after vaginal delivery)[11], and has increased risk for complications in subsequent pregnancies[12].

Some answers revealed a significant difference in opinion between MFM specialists and neonatologists. The first concern of the MFM specialists is the health of the women. The first concern of the neonatologists, is to achieve a gestational age as favorable as possible for the newborn. In case 2 this difference in view is the most obvious. The MFM specialists were less inclined to prolong pregnancy and less willing to recommend a caesarean section at a periviable gestational age, because of the possible risks for the mother's health. The neonatologists were more willing to prolong the pregnancy and recommend a caesarean section, in the hope to increase the chances for newborn survival. Dutch guidelines are in place to recommend whether or not to start active neonatal management in case of spontaneous extreme preterm birth for appropriate for gestational age infants. The latest guideline dating September 2010, recommends intubation and ventilation from 24 weeks onwards and cardiac resuscitation from 25 weeks onwards. Estimated fetal weight limits are not included[13]. The American Association of Paediatrics (AAP) has established policies regarding resuscitation at the limits of viability and advises to base management decisions on an assessment of the infant's medical condition, physiologic maturity and probabilities of death and/or severe disability[14]. But they also state that, as in any pregnancy, obstetric interventions should be undertaken only after a discussion with the family on individual risks and benefits of management options. Parents should be given the choice for palliative care alongside the option to attempt resuscitation[15]. In case of preeclampsia decisions to delay delivery may result in worsening of the maternal condition and fetal growth in a compromised environment. The AAP advises health-care providers to consider these risks in the context of periviable

gestational age and expected outcome for the neonate and discuss these risks with the parents[15].

A limitation of this study is the response rate of 37% (34% of the MFM specialists and 39% of the neonatologists). We invited all registered MFM-specialists as well as all registered neonatologists, however, not all registered MFM specialists and neonatologists are employed in tertiary centers, where these women are treated. Unfamiliarity with these complicated issues might have caused the response rate of 37%. A strength of the study is that the survey was sent to the MFM-specialists and neonatologists separately. Results show a marked difference in viewpoint on whether or not to prolong pregnancies or perform a caesarean section in these cases. These differences in viewpoints should be taken into account when discussing cases in a clinical setting.

CONCLUSION

This study investigated the opinion of medical professionals on management, reporting and auditing late termination of pregnancy for maternal indications at a periviable gestational age. The majority of MFM specialists and neonatologists would be willing to report these terminations to a medical expert committee for internal audit, but not for legal assessment. We hope that the results of this study will be useful to open the discussion between professionals and promote transparency as well as a positive attitude towards reporting and auditing.

REFERENCES

1. Wetboek online. www.wetboek-online.nl/wet/Sr/82a.htlm
2. Jaarrapportage 2014 van de Wet afbreking zwangerschap. Inspectie voor de Gezondheidszorg, Ministerie van Volksgezondheid, Welzijn en Sport. www.igz.nl. Accessed 15 October 2015
3. wetboek online. www.wetboek-online.nl/ wet op de lijkbezorging
4. NVOG modelprotocol LZA: Medisch handelen late zwangerschapsafbreking 2007. www.nvog-documenten.nl/index.php
5. Regeling beoordelingscommissie late zwangerschapsafbreking en levensbeëindiging bij pasgeborenen. Staatcourant, nr 3145, 26-01-2016. www.wetten.overheid.nl/BWBR0037570
6. van Eerden L, Zeeman GG, Page-Christiaens GC et al. Termination of pregnancy for maternal indications at the limits of fetal viability: a retrospective cohort study in the Dutch tertiary care centres. BMJ open 2014 Jun 17;4 (6):e005145
7. wetboek online. www.wetboek-online.nl/wet medisch wetenschappelijk onderzoek met mensen
8. Belghiti J, Kayem G, Tsatsaris V et al. Benefits and risks of expectant management of severe pre-eclampsia at less than 26 weeks gestation: the impact of gestational age and severe fetal growth restriction. Am J Obstet Gynecol 2011;205:465.e1-6.
9. Schutte J, Steegers E, Schuitemaker N et al. on behalf of The Netherlands Maternal Mortality Committee. Rise in maternal mortality in the Netherlands. BJOG 2010;117:399–406.
10. Knight, M; Kenyon, S; Brocklehurst et al. on behalf of MBRRACE-UK, Saving Lives, Improving Mothers' Care Lessons learned to inform future maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009-2012.
11. Reddy UM, Rice MM, Grobman WA et al. Serious maternal complications after early preterm delivery (24-33 weeks' gestation). Am J Obstet Gynecol 2015;213:538.e1-9.
12. Lannon SMR, Guthrie KA, Vanderhoeven JP et al. Uterine rupture risk after periviable cesarean delivery. Obstet and Gynecol 2015 125;5:1095-1100
13. Nederlandse richtlijn perinataal beleid bij extreme vroeggeboorte. www.nvog-documenten.nl/index.php
14. American Association of Paediatrics, Committee on Fetus and Newborn. Noninitiation or withdrawal of intensive care for high-risk newborns. Pediatrics.2007;119(2):401-403
15. Periviable birth. Obstetric Care Consensus No. 3. American College of Obstetricians and Gynecologists. Obstet Gynecol 2015;126:e82e94

Part II

Indicated delivery for hypertensive disorders at the limits of fetal viability with the intention to intervene for fetal indications and active neonatal management

Chapter 6

Maternal and neonatal outcomes in women with severe early onset preeclampsia before 26 weeks of gestation, a retrospective cohort study

MF van Oostwaard, L van Eerden, MW de Laat,
JJ Duvekot, JHM Erwich, KWM Bloemenkamp, AC Bolte,
JPF Bosma, SV Koenen, RF Kornelisse, B Rethans,
P van Runnard Heimel, HCJ Scheepers, W Ganzevoort,
BWJ Mol, CJM de Groot, IPM Gaugler-Senden

BJOG 2017; Aug;124(9):1440-1447

ABSTRACT

Objective

To describe the maternal and neonatal outcomes and prolongation of pregnancies with severe early onset preeclampsia before 26 weeks' gestation.

Design

Nationwide retrospective cohort study.

Setting

All Dutch tertiary perinatal care centres.

Population

All women, diagnosed with severe preeclampsia, who delivered between 22 and 26 weeks' gestation in a tertiary perinatal care centre in the Netherlands between 2008 and 2014.

Methods

Patients were identified through computerized hospital databases. Data were collected from medical records.

Main Outcome Measures

Maternal complications (HELLP syndrome, eclampsia, pulmonary oedema, cerebrovascular incidents, hepatic capsular rupture, placenta abruption, renal failure or maternal death), neonatal survival and complications (intraventricular haemorrhage, retinopathy of prematurity, necrotizing enterocolitis, bronchopulmonary dysplasia and sepsis) and outcome of subsequent pregnancies (recurrent preeclampsia, premature delivery, neonatal survival).

Results

We studied 133 women, delivering 140 children. Maternal complications occurred frequently (54%). Deterioration of HELLP syndrome during expectant care occurred in 48%, after 4 days. Median prolongation after admittance was 5 days (range: 0-25 days). Neonatal survival was poor (19%) and 84% suffered from one or more complications and was worse (6.6%) if admitted before 24 weeks. Survival after active support (54%) was comparable to spontaneous premature neonates. The recurrence rate of preeclampsia was 31%, at later gestational age.

Conclusions

Women need to be counselled carefully, weighing the risk for maternal complications versus limited neonatal survival and/or extreme prematurity and its sequelae, considering the positive prospects regarding maternal and neonatal outcome in a future pregnancy.

INTRODUCTION

Preeclampsia (PE) is a common pregnancy disorder with still high maternal and neonatal mortality and morbidity. It affects 2-5% of pregnancies[1], and occurs most commonly at term. At extreme premature gestational age, severe preeclampsia and HELLP syndrome (Haemolysis, Elevated Liver enzymes and Low Platelets) are rare. At present, delivery of the fetus is the only curative treatment of hypertensive pregnancy complications, but for women with early preeclampsia this inevitably leads to extreme prematurity, with high risk of neonatal mortality and morbidity. Conversely, prolongation of pregnancy of severe early onset PE may increase the risk of maternal morbidity[2-7], but may improve fetal prognosis. These conflicting interests between mother and fetus raise a dilemma in clinical decision making. This discussion is even more pressing as fetuses in early preeclampsia are often also severely growth restricted, further limiting their chances for (healthy) survival, both intra-uterine and extra-uterine, and its associated adverse long term outcome.

In 2006, Gaugler et al[4] described high rates of major maternal complications (65%) and perinatal mortality (82%) after expectant management of pregnancies complicated by severe, very early onset PE. In line with these findings, there is consensus that prolongation of pregnancy should not be offered as routine treatment option in women with severe preeclampsia with onset <24 weeks gestational age[4,5,6,7,8]. However, this subject is debated in literature for a select group of patients that still needs to be defined[9,10].

Neonatal care and resuscitation have improved leading to a higher survival rate[11], which may make management decisions even more difficult in the time frame at the limit of neonatal viability. Improved care and survival rate resulted in a new Dutch guideline regarding active neonatal resuscitation in spontaneously born premature neonates at a gestational age beyond 24 completed weeks in September 2010[12]. Before the introduction of the guideline, active neonatal resuscitation was not generally performed before 25 weeks of gestation, unless an active resuscitation seemed justified. Expectant care for extreme early onset preeclampsia may seem defendable at an earlier gestational age in hope of neonatal survival. Iatrogenic prematurity in preeclampsia however does not resemble spontaneous premature delivery.

In this nationwide retrospective cohort study we aimed to display the maternal and neonatal outcomes and prolongation of pregnancies with severe early onset preeclampsia and delivery before 26 weeks' gestation. Secondly, we analysed trends in management and maternal and neonatal outcome over the years and analysed recurrence of PE in a subsequent pregnancy.

MATERIALS AND METHODS

Study population

This study was performed in all 10 tertiary care centers in the Netherlands. We included consecutive women who delivered between 22 and 26 weeks of gestation, between January 2008 and January 2014, and were diagnosed with severe preeclampsia. In each perinatal center we identified women from electronic databases and subsequently extracted data from their medical files. Women with a pregnancy complicated by fetal abnormalities or an intra uterine fetal death (IUFD) at admission were excluded. First trimester ultrasound dating was standard practice for determination of gestational age. The acknowledged ethical advisory board of the Academic Medical Center, Amsterdam approved the study (W13_106 # 13.17.0123).

Severe preeclampsia was defined as hypertension (diastolic blood pressure ≥110 mmHg or systolic blood pressure ≥160 mmHg on two occasions) in combination with proteinuria (defined as a protein/creatinine ratio of ≥30 mg/mmol in a random sample or a urine protein excretion of ≥300 mg per 24 hrs) with oliguria, cerebral or visual disturbances, pulmonary oedema, epigastric or upper-quadrant pain, impaired liver function, thrombocytopenia, after 20 weeks of pregnancy.[13] Chronic hypertension was defined as pre-existing hypertension or hypertension before 20 weeks of gestation. Superimposed preeclampsia includes de novo proteinuria, or a sudden increase in proteinuria if already present, in a woman with chronic hypertension.[13] HELLP syndrome was defined by haemolysis (elevated lactate dehydrogenase (LDH) levels ≥ 600 U/L), elevated liver enzymes by levels of aspartate transaminase (ASAT) or alanine transferase (ALAT) ≥ 70 U/L and low platelets < 100,000/mm.[14] Deterioration of HELLP syndrome was defined as a new rise in laboratory findings after initial recovery. Small for Gestational Age (SGA), was defined as birth weight below the 5th percentile.

After admission, women were stabilized by administration of antihypertensive therapy and in case of severe hypertension and magnesium sulphate for prevention of eclampsia. The fetal growth and condition was determined by ultrasound. Cardiotocography was performed when considered appropriate depending on ultrasound findings and gestational age. The parents were then counselled by experienced obstetric and neonatalogy staff and depending on the clinical condition of both mother and fetus, the obstetric management was determined. If active neonatal support was pursued, a course of 12 mg intramuscular betamethasone was given and repeated after 24 hours to accelerate fetal lung maturation. Initiating delivery, depending on maternal and fetal condition, was performed by induction of labour or caesarean section. An induction of labour was started in good fetal condition or when management was not aimed at survival of the foetus (termination of pregnancy). A caesarean section was reserved for cases where it was considered to improve the chances of survival in compromised fetuses or when normal delivery was not feasible (transverse position, maternal condition).

Neonates born before implementation of the new Dutch guideline regarding active neonatal resuscitation in 2010[12], were in general not offered active support before $25^{0/7}$ weeks of gestation. After the new guideline active support from a gestational age of $24^{0/7}$ was optional, but could be refrained from in case of poor foetal prognosis. Counseling of future parents on maternal and neonatal management was performed by gynaecologists and neonatologists.

Maternal data included: maternal age at delivery, parity, medical and obstetric history and cardiovascular risk factors like: smoking, body mass index (BMI) before pregnancy, chronic hypertension diagnosed before pregnancy and thrombophilia. We recorded pregnancy data (e.g. maximal blood pressures, proteinuria, maximal laboratory abnormalities, use of medication, HELLP syndrome at admission, mode of delivery and complications. Maternal complications were defined as: HELLP syndrome (appearing or deteriorating after admission), eclampsia, pulmonary oedema (clinical and radiographic diagnosis), cerebrovascular incidents, hepatic capsular rupture, placenta abruption, renal failure (with need for dialysis) and maternal death. We documented the interval between admission and delivery and the indication for delivery. intra uterine fetal death (IUFD)). Neonatal data included: gestational age at birth, birth weight, sex, perinatal death and complications. Neonatal complications if admitted to a Neonatal Intensive Care Unit (NICU) were defined as: Intraventricular Haemorrhage (IVH) (defined as ≥ grade 3, according to Papile et al[15]), retinopathy of Prematurity (ROP) (defined as ≥ grade 3 in accordance with the International Classification for ROP)[16], Necrotizing Enterocolitis (NEC) (defined as ≥ stage 2 in accordance with the staging by Bell et al[17]), Bronchopulmonary Dysplasia (BPD) (classified according to the consensus BPD definition[18] as moderate if the oxygen need (FiO2) at 36 weeks postmentrual age is between 0.21 and 0.30, and severe in case of a FiO2 > 0.30 and/or receiving continuous positive airway pressure (CPAP) or mechanical ventilation) and sepsis (defined as the presence of clinical symptoms and a positive blood culture).

If information on a subsequent pregnancy was available, these data were also documented.

Statistical analysis

Statistical analysis was performed using SPSS 23.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as means with standard deviations (SD) or medians with interquartile ranges (IQR). We compared women undergoing expectant management and women having immediate delivery. Differences in baseline characteristics or outcomes between groups were tested with parametric (unpaired t-test) or non-parametric (Mann-Whitney-U test) tests as appropriate. Categorical variables were compared with Chi square tests. P values less than 0.05 were considered to indicate statistical significance. Differences in maternal and perinatal outcome were assessed using multivariable logistic regression analysis. We corrected for the following confounders: parity, maternal

		N = 133
Demographic characteristics:		
Maternal age at delivery (years)		31 (5.7)
Smoking		11 (8.3%)
Body mass index, BMI (kg/m^2)		28 (6.5)
Chronic hypertension before pregnancy		35 (26%)
History of disease	- Obesity (BMI> 30)	34 (26%)
	- Pulmonary disease	6 (4.5%)
	- Thrombophilia	4 (3.0%)
	- Kidney disease	3 (2.3%)
	- Diabetes Mellitus	2 (1.5%)
	- Coronary disease	2 (1.5%)
	- SLE	1 (0.8%)
	- Other*	12 (9.0%)
Obstetrical history:		
Nulliparous		85 (64%)
Multiparous		48 (36%)
Preeclampsia in a former pregnancy		21 (44%)
Multiple pregnancy		3 (8.8%)
Clinical syndrome:		
Preeclampsia		133 (100%)
HELLP syndrome at admittance		42 (32%)
Maximum blood pressure (mmHg)	- Systolic	179 (20)
	- Diastolic	111 (11)
Maximal laboratory abnormalities	- ASAT (IU/L)	193 (38 - 159)
	- Platelets (*10^9/L)	90 (57 - 157)
	- Proteinuria (mg/24h)	1028 (393 - 3790)
	- PCR**	195 (37 - 431)
Use of medication	- oral antihypertensive	117 (88%)
	- iv antihypertensive	107 (81%)
	- iv anticonvulsive	120 (90%)
Gestational age at admittance (wks+ days)		$24^{0/7}$ ($23^{1/7}$ – $24^{5/7}$)
Gestational age < 24 weeks		61 (46%)
Estimated fetal weight at admittance (grams)		479 (125)
Abnormal umbilical artery Doppler flow		92 (72%)

Table 1. Continuous data are presented as means (SD); lab abnormalities and gestational ages in median (IQR)

* Other medical history: hemoglobinopathy (3), HIV, thrombotic thrombocytopenic purpura, hypothyroidism, Cohn's disease, sarcoidosis, mixed connective tissue disease and cutaneous lupus erythematosus

** PCR: Protein / Creatinin Ratio, registered if a 24 hour collection of urine was not performed (N=17)

age, medical history, gestational age at admittance, maximal blood pressures, maximal laboratory abnormalities and estimated fetal weight. Using the 'enter method' in the regression analysis, no selection or hierarchy of the confounders was made, since we are unaware which confounder would affect the outcome most. Outcomes are shown as odds ratios (OR) with 95% confidence interval (95%CI).

RESULTS

During the study period, 133 women fulfilled the inclusion criteria, including 8 multiple pregnancies, delivering 140 neonates. In one woman with a multiple pregnancy, an IUFD was discovered of one of the fetuses at 16 weeks and was considered a singleton pregnancy in the neonatal analyses. Baseline characteristics are shown in Table 1. Most women were nulliparous (64%). At admittance, the median gestational age was $24^{0/7}$ (IQR: $23^{1/7}$ – $24^{5/7}$) and 61 women (46%) had a gestational age of less than 24 weeks. HELLP syndrome was present in 42 women (32%) at time of admission.

An overview of management is shown in Figure 1. After admission, 22 (17%) intrauterine fetal deaths occurred, after which labor was induced. Delivery was indicated for maternal reasons in 85 (64%) women and for fetal indication in 26 (20%). Maternal indication for delivery existed of worsening maternal condition, based on: complica-

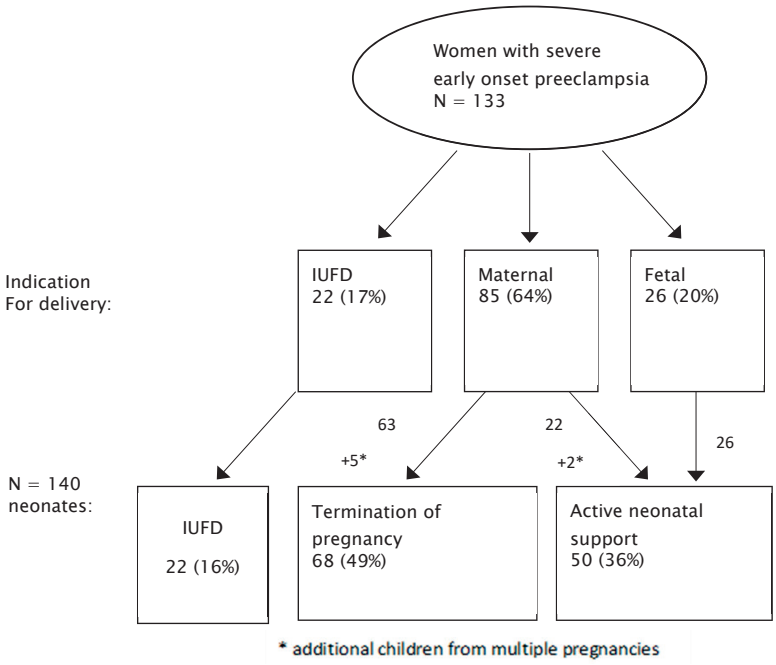


Figure 1. Overview of management in the 133 pregnancies with severe, early onset preeclampsia.

		N = 133
Interval between admittance and delivery		5 (3 - 9)
Gestational age at delivery (wks+days)		$25^{0/7}$ ($24^{2/7}$ – $25^{4/7}$)
Gestational age < 24 weeks		20 (15%)
Caesarean Section		48 (36%)
Hospitalization (days)		10 (7 - 14)
Maternal complications	- HELLP syndrome appearing or deteriorating after admission:	64 (48%)
	- Eclampsia	4 (3%)
	- Lung oedema	10 (7.5%)
	- CVA	0 (0%)
	- Placental Abruption	5 (3.8%)
	- Hepatic capsular rupture	1 (0.8%)
	- Renal failure	1 (0.8%)
	- Maternal death	0 (0%)
	- Other*	7 (5.3%)
	- Any complication	72 (54%)
	(- Any complication including HELLP at admission)	91 (68%)
All neonates:		**N = 140**
Male - female		65 - 75 (46 - 54%)
Birth weight (grams)		500 (127)
Small for Gestational Age		80 (57%)
Completed course lung maturation		58 (41%)
Active neonatal support		50 (36%)
- IUFD		22 (16%)
- Intrapartum death (termination of pregnancy)		68 (49%)
- Neonatal death ≤ 7 days		13 (8.5%)
- Perinatal death (all the above)		103 (74%)
- Neonatal death > 7 days		10 (7.9%)
- Total mortality		113 (81%)
- Total survival		27 (19%)
Active neonatal support:		**N = 50**
- NICU admission		48 (96%)
- Total mortality after active support		23 (46%)
- Total survival after active support		27 (54%)

Table 2. Outcomes of the 133 women and 140 neonates after severe early onset preeclampsia. Continuous data are presented as means (SD); interval between admittance and delivery, gestational ages and hospitalization in median (IQR)
Significant differences are indicated in bold.
* Other maternal complications: infection, cardiac decompensation, haemorrhagia postpartum

tions, deteriorating laboratory findings in HELLP syndrome and uncontrollable blood pressures. Also, fetal condition played a role in the timing of delivery. In 63 women this resulted in a termination of pregnancy and in 22 women active support was offered to the child(ren). In one case spontaneous preterm labor followed 5 days after admittance, which was classified as maternal indication.

Maternal and neonatal outcome

Table 2 shows outcomes of women and neonates. The median interval between admittance and delivery was 5 days (IQR: 3 - 9) with a range of 0 to 25 days. In 107 women (80%) this prolongation was more than 2 days. The median gestational age at delivery was $25^{0/7}$ (IQR: $24^{2/7}$ – $25^{4/7}$). Maternal complications occurred in 72 women (54%) and consisted of (new, deteriorating or postpartum) HELLP syndrome, eclampsia, lung oedema, placental abruption, hepatic capsular rupture renal failure and other (infection, cardiac decompensation, haemorrhagia postpartum). HELLP syndrome occurred in 83 women (62%). In 42 women (51%) HELLP was already present at time of admittance, which deteriorated in 22 (52%) during hospitalization. In 38 women (46%), the HELLP syndrome appeared after admission. Appearance or deterioration of HELLP syndrome after admission (63 women) occurred after a median of 4 days from admittance and in 2 women (2.4%) the HELLP syndrome occured postpartum. A completed course of betamethasone for fetal lung maturation was given in 52 women (58 neonates). An intended course could not be completed due to deterioration of maternal or fetal condition in 4 women (7.7%). Active neonatal support was offered in 50 neonates (36%), of whom 27 (54%) survived (neonatal survival of was 19% in the total cohort). Only 4 (6.6%) neonates survived after admission before 24 weeks gestational age. Caesarean sections were performed in 48 women (36%), 24 (51%) for fetal indication, and after which 46 (96%) neonates were offered active support. Perinatal death occurred in 21 (44%) after caesarean section.

The incidence of neonatal complications in the 27 surviving children is shown in Table 3. Surviving neonates experience complications in 84%. Neonatal mortality was associated with NEC in 5 (19%), sepsis in 11 (41%), IVH in 5 (19%) and infant respiratory distress syndrome (IRDS) in 5 neonates (19%), mostly in combinations. Other complications leading to neonatal death consisted of: arrhythmia, intracardial thrombus and multi-organ failure.

Maternal and neonatal outcome in relation to gestational age at admittance is presented in Table 4. From admission before $22^{6/7}$ weeks of gestation to admission between 25 and 26 weeks gestation, the median interval between admittance and delivery ranged from 9.5 to 3.5 days, Caesarean section rates ranged from 12 to 75% and total perinatal death (with or without active support) ranged from 96% to 52%. Maternal complications ranged from 38 to 58%. Neonatal complications ranged from 80 to 100%.

Neonatal complications	N (%)
- IVH ≥ grade 3	1 (4%)
- ROP ≥ grade 3	4 (21%)
- NEC ≥ stage 2	3 (12%)
- BPD – moderate	13 (48%)
- BPD – severe	7 (28%)
- Sepsis	15 (56%)
- Other*	16 (60%)
- Any complication	22 (84%)

Table 3. Neonatal complications in the 27 surviving children.
*Other neonatal complications: patent arterial duct, cerebellar haemorrhage, lung bleeding, focal bowel perforation.

Surviving neonates versus non surviving neonates

Gestational ages at delivery of the 27 pregnancies with surviving children in the total cohort were on average 7 days longer ($24^{6/7}$ versus $23^{6/7}$, p-value<.001) than the non-surviving neonates (N=106). Furthermore, the estimated fetal weight at admittance was higher (598 versus 454 grams, p-value: <.001) and children were less often SGA (30% versus 68%, p-value: <.001) and had less often abnormal umbilical artery Doppler flow (52% versus 78%, p-value: .011) than non-surviving neonates. Of the 27 surviving neonates, 26 were delivered by Caesarean section. Neonatal sex did not affect survival (male: 37% versus 49%, p-value: .264). The clinical maternal syndrome was not significantly different regarding maximal blood pressures, maximal laboratory abnormalities and medication.

Trends in prolongation

We investigated prolongation in more detail. Prolongation, presented as time between admittance and delivery in relation to gestational age at admittance, and survival of the neonate can be seen in Figure 2A. In the course of the study period, implementation of a new guideline[12] for neonatal support allowed to shift the minimal gestational age for active neonatal support from $25^{0/7}$ to $24^{0/7}$ weeks. Disregarding the year 2010 as year of transition, we compared prolongation time from admittance to delivery between the years 2008 – 2009 and 2011 – 2013 in Figure 2B. The median prolongation after 2010 was 5 days, which equals the median prolongation before 2010.

GA at admission Wks+days	N mothers (children)	Median interval admittance to delivery days (IQR)	Gestational age at delivery Weeks+days (IQR)	Course of betamethasone n (%)	Caesarean section n (%)	Maternal complications	n (%)	Active neonatal support n (%)	Perinatal death	n (%)	Neonatal complications	n (%)
						HELLP syndrome:	10 (38)		IUFD:	9 (32)	Survival: 1 (4)	
						Pulmonary oedema:	1 (3.8)		TOP:	17 (61)	BPD:	1 (100)
< $22^{6/7}$	26 (28)	9.5 (4 - 18)	$23^{3/7}$ ($22^{6/7}$ - $24^{6/7}$)	2 (7.7)	3 (12)	Abruption:	1 (3.8)	2 (7.1)	Neonatal <7d:	1 (3.6)	**Any:**	**1 (100)**
						Other:	1 (3.8)		**Total:**	**27 (96)**		
						Any:	**11 (42)**					
						HELLP syndrome:	18 (51)		IUFD:	6 (16)	Survival: 4 (10)	
						Pulmonary oedema:	2 (5.7)		TOP:	20 (52)	ROP:	2 (50)
$23^{0/7}$ – $23^{6/7}$	35 (38)	9.0 (4 - 11)	$24^{5/7}$ ($24^{1/7}$ – $25^{0/7}$)	15 (43)	9 (26)	Abruption:	1 (2.9)	10 (26)	Neonatal <7d:	7 (18)	BPD:	4 (100)
						Other:	5 (14)		Neonatal >7d:	1 (2.6)	Sepsis:	2 (50)
						Any:	**20 (57)**		**Total:**	**34 (90)**	**Any:**	**4 (100)**
						HELLP syndrome:	25 (52)		IUFD:	7 (14)	Survival: 10 (20)	
						Pulmonary oedema:	4 (8.3)		TOP	23 (47)	IVH:	1 (10)
						Abruption:	3 (6.3)		Neonatal <7d:	4 (8.2)	ROP:	1 (10)
$24^{0/7}$ – $24^{6/7}$	48 (49)	5.0 (3 - 6)	$25^{1/7}$ ($24^{5/7}$ – $25^{2/7}$)	23 (48)	18 (38)	Eclampsia:	1 (2.1)	19 (39)	Neonatal >7d:	5 (10)	NEC:	3 (30)
						Other:	1 (2.1)		**Total:**	**39 (80)**	BPD:	7 (70)
						Any:	**28 (58)**				Sepsis:	5 (50)
											Any:	**8 (80)**
						HELLP syndrome:	5 (21)		IUFD:	1 (4)	Survival: 12 (48)	
						Postpartum HELLP:	2 (8.3)		TOP:	5 (20)	ROP:	1 (8.3)
						Pulmonary oedema:	3 (13)		Neonatal <7d:	3 (12)	BPD:	8 (67)
$25^{0/7}$ – $26^{0/7}$	24 (25)	3.5 (2 - 5)	$25^{6/7}$ ($25^{5/7}$ – $26^{0/7}$)	19 (79)	18 (75)	Liver hematoma:	1 (4.2)	19 (76)	Neonatal >7d:	4 (16)	Sepsis:	8 (67)
						Renal failure:	1 (4.2)		**Total:**	**13 (52)**	**Any:**	**10 (83)**
						Eclampsia:	3 (13)					
						Any:	**9 (38)**					

Table 4. Prolongation and maternal and neonatal outcome in relation to gestational age at admission.

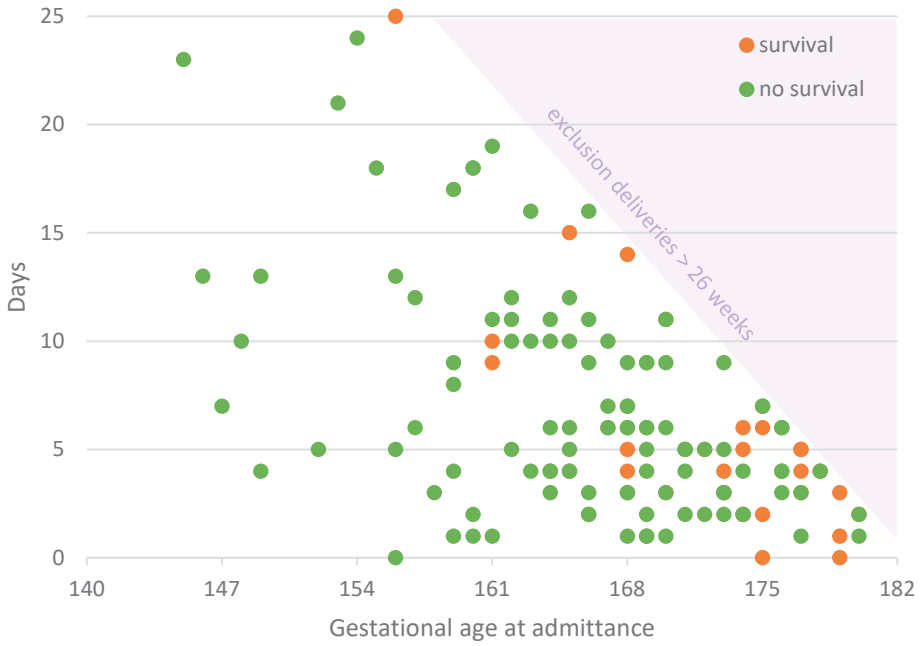


Figure 2A. Interval from admission to delivery

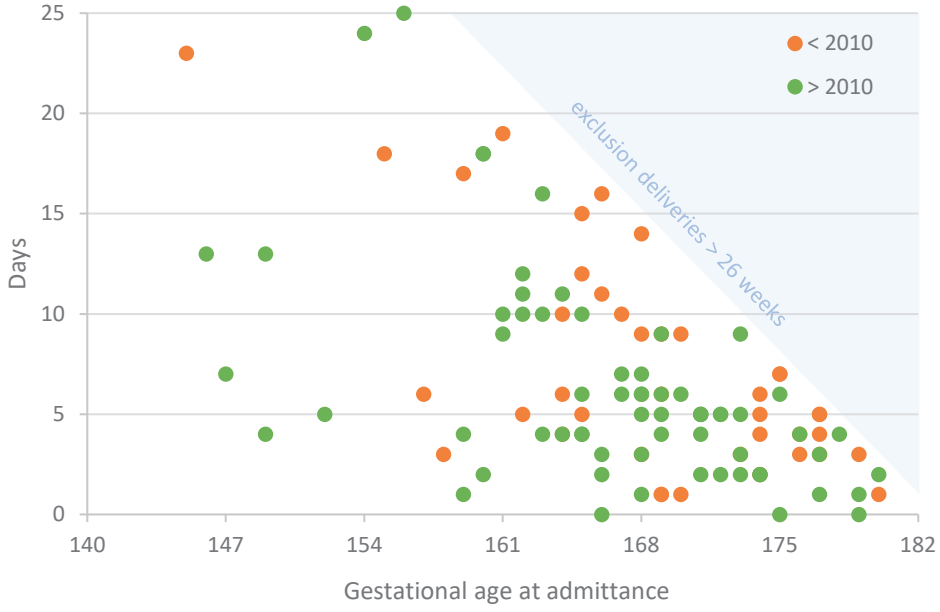


Figure 2B. Interval from admission to delivery before and after 2010

Trends in maternal and neonatal outcome

Maternal and neonatal outcome in the course of the study period is shown in Figure 3. The occurrence of maternal complications decreased from 65-75% to 41% during the study period and neonatal survival after active neonatal support fluctuated between 40 and 80%. Most surviving neonates (21 of 27) were born between 25 and 26 weeks of gestation. Only 6 neonates born between 24 and 25 weeks (after 2010) survived. The Caesarean section rate peeked to 62% in 2011, while it ranges from 26 to 38% in the remaining years of the study period. Only one (8.3%) Caesarean section was performed at a gestational age before 24 weeks (2013). In women with a gestation before 25 weeks (n=41), 9 (22%) Caesarean sections were performed.

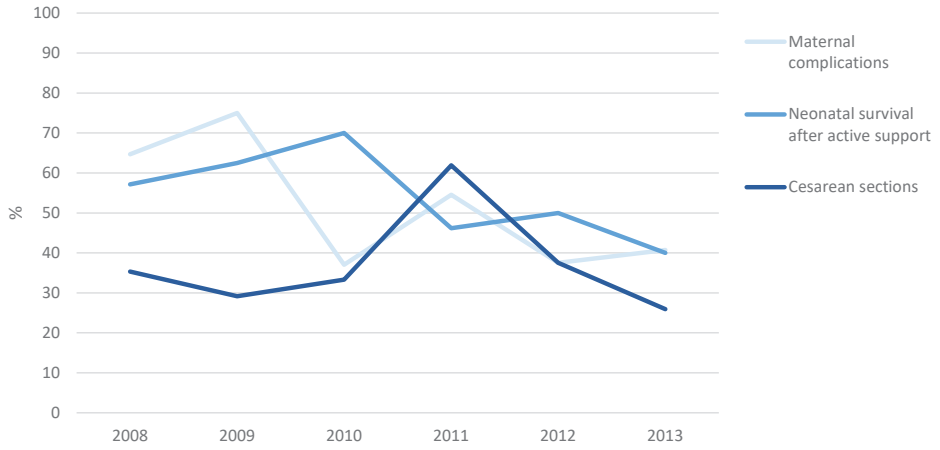


Figure 3. Trends in maternal complications, neonatal survival and Cesarean sections. Maternal complications: HELLP syndrome, eclampsia, pulmonary oedema, cerebrovascular incidents, liver bleeding, placenta abruption, kidney failure with need for dialysis and maternal death.
N= 133 women (2008: N=17, 2009: N=24, 2010: N=27, 2011: N=22, 2012: N=16, 2013: N=27)
Active support: N= 50 neonates (2008: N=7, 2009: N=8, 2010: N=10, 2011: N=14, 2012: N=6, 2013: N=5)

Subsequent pregnancies

Forty-two women (32%) of the 133 women in this cohort were lost to follow up and information on subsequent pregnancies could not be obtained. A subsequent pregnancy occurred in 61 women (67%), of whom 2 miscarried. We had complete data of 55 ongoing pregnancies. They delivered again after a mean of 20 months (SD: 10 months) after the index delivery, at a mean gestational age of 35 weeks and 4 days (SD: 36 days).

Of the 55 subsequent pregnancies, 17 (31%) women had recurrent preeclampsia (mean GA: $32^{6/7}$, SD: 38 days) of which 3 pregnancies were complicated by HELLP (18%). Four women (7.3%) delivered before 28 weeks again. Perinatal death occurred in 5 (9.6%) subsequent pregnancies: 2 pregnancies were terminated (trisomy 18 and foetal

intracerebral haemorrhage), in 2 other pregnancies IUFD occurred and one neonatal death was associated with severe growth restriction. Eventually, 50 women (91%) had a living child from the subsequent pregnancy.

DISCUSSION

Main findings

In the Netherlands, women with severe early onset preeclampsia are delivered mostly for maternal reasons after a median prolongation of 5 days, which was unaffected by the implementation of the new guideline for active neonatal support. Maternal complications occurred frequently (54%) and neonatal survival was limited (19%) and troubled by complications (85%). Neonatal survival after active support (54%) was comparable to spontaneous premature born children. Surviving neonates were on average 7 days older and their weight was estimated 144 grams more than non-surviving neonates. The recurrence rate of preeclampsia was 31%, however at significant later gestational age (mean: $32^{6/7}$) with 91% neonatal survival.

Strengths and limitations

This contemporary nationwide cohort is unique as all Dutch perinatal centres participated in this study, and we were therefore able to include all women who met the inclusion criteria. Data collection was complete since we collected information from the medical files.

Baseline characteristics show serious illness of the mother and compromised fetal condition as expected. New developing or deterioration of HELLP syndrome (63 women) contributed to the maternal reason to deliver after expectant management. Wether HELLP syndrome or deterioration of HELLP syndrome could have been prevented by prompt delivery is unknown.

There are several sources of potential bias that hinder too firm conclusions. First, the size of the cohort is rather small, in line with the rarity of this extreme condition and similar even smaller published cohorts[4-7]. Furthermore, retrospective nature of this cohort and the fact that we were unable to retrieve the reasons behind the different management regimes do not allow meaningful comparison of outcomes between groups of expectant care or immediate delivery. Finally, women were selected for gestational age at delivery rather than gestational age at decision for management regime, inducing an information gap of women who are admitted before, but delivered after 26 weeks.

Interpretation

In this study we describe outcome of women and their children with severe early onset preeclampsia. The overall maternal complication rate of 68% (including HELLP syndrome at admittance) is comparable to literature[4-7]. In contrast to other literature, our study presents appearance of or deterioration of HELLP syndrome after admittance, which can be regarded as a complication of expectant management. Although a decreasing trend may be seen in the occurrence of maternal complications over the study period, it is too soon to draw any conclusions about the reasons. Perinatal mortality and neonatal complications are also comparable to literature on severe early onset preeclampsia[4-7]. However, compared to perinatal death rates of 45% in extreme premature neonates in a Swedish nationwide cohort[11] without maternal preeclampsia, perinatal death was much higher in our cohort. This concurs with the concept that neonates born from mothers with severe early onset preeclampsia are not comparable to spontaneous premature born children. On the other hand, the neonatal survival rate after active support (27/50, 54%) is comparable to the results of the Swedish study[11]. Neonatal survival after extreme premature preeclampsia in this cohort does not seem to have improved over recent years. From 2010 active support is offered at an earlier gestational age, which may have effect on survival.

In 80% of the women included in this study, prolongation was 3 days or more, despite the high maternal complication rate and perinatal mortality. Prolongation time between admittance and delivery was in general 5 days, which is comparable to the results of some studies[5,6]. In other studies much longer prolongation of up to 32 days is reported[4,7,10]. In contrast to our cohort, only women eligible for expectant care were selected in these studies. As can be seen in Table 4 and Figure 2A, survival is very limited when presenting before 24 weeks, despite prolongation. Sibai[10] and Ganzevoort[8] reviewed the different management regimes in literature. They conclude that before 24 weeks of gestation, because of the absence of perinatal benefits and high maternal complication rate, an expectant management approach should not be offered routinely. Our findings endorse this consensus. Prolongation should only be offered to a select group of women (that still needs to be defined), in whom it is believed to benefit the neonatal prognosis, preferably after 24 weeks at presentation. In our study, maternal complications, perinatal death and neonatal complications after 24 weeks were still very high and in 85 women (64%), active neonatal support was never offered (59 neonates) despite prolongation, as their foetus was not considered viable. In line with other studies, this study does not provide selection criteria of women who are eligible for expectant care. Presented differences between pregnancies with and without surviving neonates could give guidance to counselling on this matter.

Although we have to keep in mind that the number of patients due to the rareness of this clinical dilemma does not warrant too firm conclusions, trend analyses shows a

peak Caesarean section rate in 2011. These findings could suggest a subtle influence of this guideline, with presumed better neonatal survival chances after 25 weeks and after Caesarean section.

In general, women need to be counselled carefully, weighing the risk for maternal complications versus high perinatal mortality.

CONCLUSION

Severe preeclampsia at extreme premature gestational age is a rare but serious condition with high rates of maternal and neonatal complications and perinatal death. Prolongation of more than 2 days was often applied in the Netherlands, despite the consensus in international literature that prolongation of pregnancy should not be offered as routine treatment option. Prolongation does not necessarily lead to fetal viability. Women need to be counselled carefully, weighing the risk for maternal complications versus limited neonatal survival and/or extreme prematurity and its sequelae. Estimated fetal weight, growth restriction and Doppler abnormalities should be taken into account. Furthermore, we should also provide information on the positive prospects regarding maternal and neonatal outcome in a future pregnancy.

REFERENCES

1. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. Lancet 2005;365:785-799.
2. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. Lancet 2010;376:631-44.
3. Sibai BM, Akl S, Fairlie F, Moretti M. A protocol for managing severe preeclampsia in the second trimester. Am J Obstet Gynecol 1990 Sep;163(3):733-8.
4. Gaugler-Senden IP, Huijssoon AG, Visser W, Steegers EA, de Groot CJ. Maternal and perinatal outcome of preeclampsia with an onset before 24 weeks' gestation. Audit in a tertiary referral center. Eur J Obstet Gynecol Reprod Biol 2006;128:216-21.
5. Belghiti J, Kayem G, Tsatsaris V, Goffinet F, Sibai BM, Haddad B. Benefits and risks of expectant management of severe preeclampsia at less than 26 weeks gestation: the impact of gestational age and severe fetal growth restriction. Am J Obstet Gynecol 2011 Nov;205(5):465.e1-6.
6. Bombrys AE, Barton JR, Nowacki EA, Habli M, Pinder L, How H, Sibai BM. Expectant management of severe preeclampsia at less than 27 weeks' gestation: maternal and perinatal outcomes according to gestational age by weeks at onset of expectant management. Am J Obstet Gynecol 2008;199:247.e1–247.e6.
7. Budden A, Wilkinson L, Buksh MJ et al. Pregnancy outcome in women presenting with preeclampsia at less than 25 weeks gestation. Aust N Z J Obstet Gynaecol 2006;46 407–412.
8. Ganzevoort W, Sibai BM. Temporising versus interventionist management (preterm and at term). Best Pract Res Clin Obstet Gynaecol 2011 Aug;25(4):463-76.
9. Hall DR, Odendaal HJ, Steyn DW, Grové D. Expectant management of early onset, severe preeclampsia: maternal outcome. BJOG 2000 Oct;107(10):1252-7.
10. Sibai BM, Barton JR. Expectant management of severe preeclampsia remote from term: patient selection, treatment, and delivery indications. Am J Obstet Gynecol 2007;196:514.e1-514.e9.
11. EXPRESS Group, Fellman V, Hellström-Westas L, Norman M, Westgren M, Källén K, Lagercrantz H, Marsál K, Serenius F, Wennergren M. One-year survival of extremely preterm infants after active perinatal care in Sweden. JAMA 2009 Jun 3;301(21):2225-33.
12. Richtlijn Perinataal beleid bij extreme vroeggeboorte, 15 september 2010, website NVOG: www.nvog.nl
13. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. American College of Obstetricians and Gynecologists Int Gynaecol Obstet 77(1) (2002) 67-75.
14. B.M. Sibai. The HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets): much ado about nothing? Am J Obstet Gynecol 162(2) (1990) 311-316.

Chapter 7

Mode of delivery in severe preeclampsia prior to 28 weeks' gestation, a systematic review

L van Eerden, IPM Gaugler-Senden, R de Vries,
GG Zeeman, CJM de Groot and AC Bolte

Obstetrical & Gynecological Survey, 2018; 73: 469-474

ABSTRACT

Importance

Preeclampsia with an onset prior to 28 weeks' gestation poses dilemmas for the obstetrician with regard to mode of delivery.

Objective

To analyze the success rate of attempted vaginal delivery and the maternal and neonatal outcome according to mode of delivery in women with preeclampsia and an indicated delivery prior to 28 weeks' gestation.

Evidence Acquisition

A comprehensive search was performed in the bibliographic databases PubMed, Embase.com and Wiley Cochrane Library. Main outcome was success rate of attempted vaginal delivery. Secondary outcomes were maternal and neonatal outcomes.

Results

Eight studies, describing a total of 800 women were included. Success rates of vaginal delivery varied from 1.8% to 80% and rates for cesarean section after induction of labor varied from 13% to 51%. The rates for planned cesarean section varied from 0% to 73%. Two studies (n= 53) described no statistical significant differences in maternal outcomes. Two other studies (n= 107) report no statistical difference in neonatal outcome.

Conclusions

Studies that report the success rate of attempted vaginal delivery are limited in size. However, giving the available evidence in the reported studies a trial of labor is a considerable option in counseling women with a pregnancy complicated by preeclampsia prior to 28 weeks' gestation due to the similar maternal and neonatal outcome. No differences in maternal or neonatal outcome were attributed to the mode of delivery, however, numbers are small.

INTRODUCTION

Preeclampsia occurs in approximately 5% of all pregnancies and is accountable for approximately 62.000 to 77.000 deaths worldwide each year[1]. Late onset preeclampsia (onset after 34 weeks' gestation) is more prevalent compared to early onset preeclampsia, 2.7% versus 0.3% respectively[2]. Since the disease is progressive, delivery is, for now, the only therapeutic option to prevent worsening of the maternal condition. When preeclampsia develops very early in pregnancy it poses several dilemmas for the obstetrician with regard to timing and mode of delivery. In the context of early onset preeclampsia delivery may be delayed for corticosteroid administration to benefit fetal lung maturation[3]. When delivery is indicated for either progressive maternal disease or fetal distress and can no longer be delayed, the obstetrician has to decide on the optimal mode of delivery with the best outcome for both the woman and her neonate in mind.

Some experts recommend scheduled cesarean delivery (CD) in severe early onset preeclampsia (onset prior to 28 weeks' gestation), due to the high frequency of non-reassuring fetal heart rate tracings, fetal malpresentation and often unfavorable cervix[4], whereas others recommend a trial of vaginal delivery (VD) by cervical ripening[5].

We aimed to analyze the success rate of attempted VD in severe early onset preeclampsia prior to 28 weeks' gestation using a systematic review. Secondary outcomes are maternal and neonatal outcome for the mode of delivery in women with preeclampsia prior to 28 weeks' gestation.

METHODS

A review protocol was developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)-statement (www.prisma-statement.org). A comprehensive search was performed in the bibliographic databases PubMed, Embase.com and Wiley Cochrane Library from inception up to June 2nd 2017, in collaboration with a medical librarian.

The following terms were used (including synonyms and closely related words) as index terms or free-text words: "preeclampsia", "pregnancy-induced hypertension", "pregnancy outcome", "obstetric delivery", "cesarean section", "timing of delivery", "mode of delivery". The search was performed without date, language or publication status restriction. All titles were screened and appropriate abstracts reviewed. Duplicate articles were excluded. The full search strategies for all databases can be found in the Supplementary Information.

The first two authors (LvE, IG) independently assessed all identified studies and in case of disagreement the study was assessed by a third author (AB) and a final decision on

inclusion was made. Data was extracted using a data extraction sheet specifically designed for this review. When information was unclear, the authors of the original papers were contacted for further information. For all studies the risk of bias was assessed using the Newcastle-Ottawa scale for non-randomized trials[6] (see supplemental table 4).

The main outcome was mode of delivery and comprised: scheduled CD, CD after attempted induction of labor and VD after induction of labor. Maternal outcome according to mode of delivery comprised: maternal death, ICU admission, postpartum hemorrhage > 1 liter, placental abruption and manual removal of placenta. Neonatal outcomes according to delivery route were: neonatal death, neonatal morbidity (composite outcome) and live discharge from NICU. The composite neonatal outcome comprises: birth injury, bronchopulmonary dysplasia, retinopathy, intracranial hemorrhage, necrotizing enterocolitis and neonatal seizures.

RESULTS

We identified 2384 articles, 789 in Pubmed, 1460 in Embase en 135 in the Cochrane Library. After exclusion of duplicates we assessed the title and abstract of 1657 articles, of which 1552 records did not study preeclampsia, nor studied mode of delivery nor investigated preeclampsia with onset prior to 28 weeks' gestation. Of the remaining105 articles we assessed the full text. After reading the full text, another 97 articles were excluded (Figure 1).

No RCT's were found. Eight studies, 5 retrospective cohort studies, 2 prospective cohort studies and 1 cross-sectional study, describing a total of 800 women were included in this review[7-14].

After evaluating the evidence in the selected articles, the results of 3 of the articles could not be used for this review although the articles met the selection criteria (table 1).

The manuscripts by Reddy et al[7] and Coppage et al[8] comprise large cohorts of women with preterm labor of which the subgroup of women with preeclampsia prior to 28 weeks' gestation was not analyzed separately. The third article by Hall et al[9] describes women with preeclampsia between 24 and 34 weeks' gestation. In that period of time (1992-1997), the lower limit of fetal viability was defined as 28 weeks' gestation and termination of pregnancy was performed should delivery be indicated prior to 28 weeks'. The authors of these 3 studies[7-9] were contacted to obtain specific information about women delivering with preeclampsia prior to 28 weeks' gestation, but this was not available.

The total number of women described in the included studies in this review article is 162 (table 1).

Author	Year	Study design	Quality*	N	Population	Results	Results included in review
Reddy UM	2012	Retrospective cohort	Good	189	Women with PE between GA 240/7 and 276/7 weeks	No results on mode of delivery or outcomes available for this specific subgroup.	No
Alanis MC	2008	Cross-sectional	Good	56	Women with PE between GA 240/7 and 276/7 weeks	26.8% IOL ->1.8% success No statistical significant difference in neonatal outcome	Yes for mode of delivery and neonatal outcome
Mashiloane CD	2002	Prospective cohort	Fair	24	Women with PE between GA 240/7 and 276/7 weeks	37% IOL -> 24% success No survivors prior to 28 weeks gestation No statistical significant difference in maternal outcome.	Yes for mode of delivery and maternal outcome
Coppage KH	2002	Retrospective cohort	Fair	114	Women with severe PE	Subgroup analysis in women with PE prior to 32 weeks: no statistical difference in neonatal outcome. No data available in subgroup prior to 28 weeks	No
Blackwell SC	2001	Retrospective cohort	Good	51	Women with PE prior to 28 weeks' gestation	53% IOL ->2% success No statistical significant difference in neonatal outcome Advice: planned caesarean section < 28 weeks' gestation due to low success rate	Yes for mode of delivery and neonatal outcome
Hall DR	2001	Prospective cohort	Fair	335	Women with PE prior to 34 weeks' gestation	Fetus < 28 weeks gestation were not considered viable. No data available on the subgroup with PE < 28 weeks' gestation	No
Nassar AH	1998	Retrospective cohort	Fair	19	Women with PE prior to 28 weeks' gestation	IOL success rate: 31.6%. No data on proportion of women who underwent planned caesarean prior to 28 weeks' gestation No statistical significant difference in maternal outcome	Yes for mode of delivery and maternal outcome
Kim LH	2009	Retrospective cohort	Fair	12	Women with PE prior to 28 weeks' gestation	Success rate of IOL: 80% No data available on neonatal or maternal outcome according to delivery route	Yes for mode of delivery

Table 1. table of evidence. * = quality measured using the Newcastle-Ottawa scale for non-randomized studies. For full description see supplemental table 1

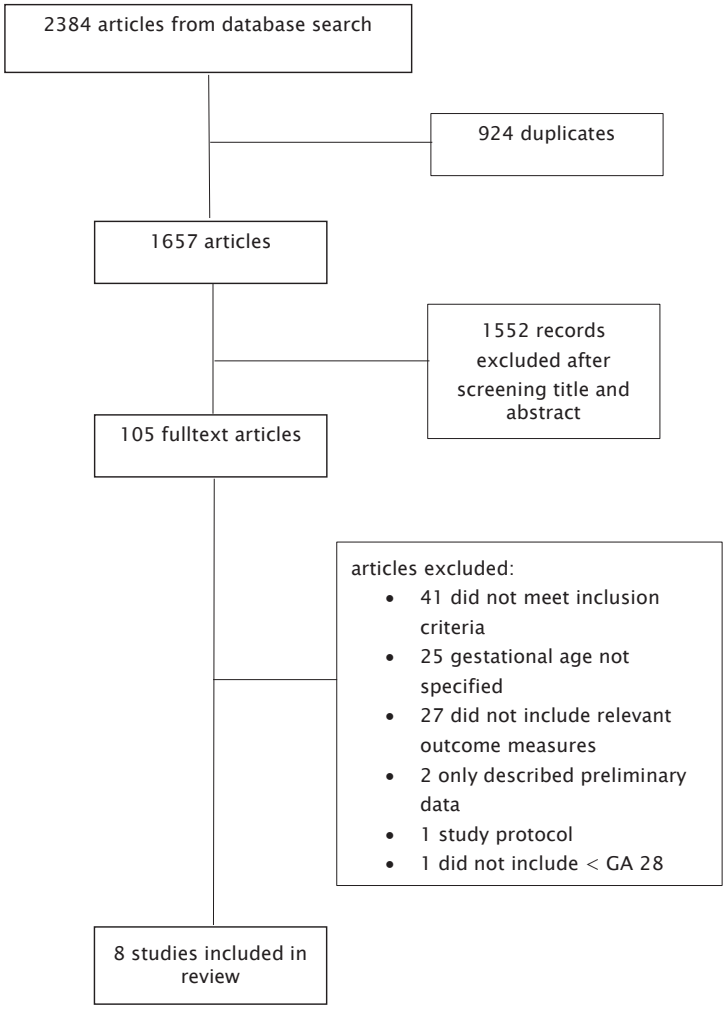


Figure 1. Flow chart: inclusion of relevant articles

Mode of delivery

There were 3 different delivery options: vaginal delivery (VD) after induction of labor, CD after attempted induction of labor and planned CD. Table 2 shows the mode of delivery per study. Success rates of VD varied from 1.8%[10] to 80%[14] and rates for CD after induction of labor varied from 13%[11] to 51%[12]. Indications for CD after attempted induction of labor were: non-reassuring fetal heart rate patterns and failure to progress. Rates for planned CD varied from 0%[14] to 73.2%[10]. Indications for planned CD were: fetal malpresentation, multiple pregnancies, unfavorable cervix (Bishop-score), non-reassuring fetal heart rate patterns, prior CD, eclampsia, placenta previa, HIV positive status, active genital herpes and intra-uterine growth restriction.

Study	Patients (N)	PCS* (%)	CS after IOL† (%)	Vaginal delivery (%)
Alanis et al	56	73.2	25	1.8
Mashiloane et al	24	63	13	24
Blackwell et al	51	47	51	2
Nassar et al	19	Unknown	Unknown	31.6
Kim et al	12	-	20	80

Table 2. Rates of delivery routes per included article. * PCS = Planned Caesarean section, † IOL = induction of labor

Maternal outcomes

None of the studies report the predefined maternal outcome; maternal death, ICU admission, placental abruption or surgical removal of the placenta.

Two studies report on maternal outcomes[11-13] (table 3); both studies report endometritis and 1 study also reports postpartum hemorrhage[11]. In both reports there was a non-significant higher incidence of endometritis in the CD after induction of labor group. Furthermore, the study by Maslihoane reports a non-significant higher rate of postpartum hemorrhage in the planned CD group[11].

			Endometritis	
Study	**PCS* (%)**	**CS after IOL† (%)**	**Vaginal delivery**	**Significance**
Mashiloane	5.9	14.3	-	NS#
Nassar		12.0	4.3	NS
			Postpartum hemorrhage	
	PSC (%)	**CS after IOL (%)**	**Vaginal delivery**	**Significance**
Mashiloane	3	-	-	NS

Table 3. Maternal outcomes according to delivery route. * PSC = Planned Caesarean section, † CS after IOL = Caesarean section after induction of labor, #NS = not significant

Neonatal outcome

Two studies report neonatal outcome by mode of delivery[10-12] (table 4). The studies report no differences in neonatal death, composite neonatal morbidity which was the predefined outcome for our study. Life discharge from NICU is not reported. The studies report no difference in birth injury between the delivery groups.

Neonatal death				
Study	**PSC (%)**	**CS after IOL (%)**	**Vaginal delivery (%)**	**Significance**
Alanis	8.6	-	2.5	NS[#]
Composite neonatal outcome[+]				
Study	**PSC (%)**	**CS after IOL (%)**	**Vaginal delivery (%)**	**Significance**
Alanis	76.1	-	51.4	NS
Blackwell	60	46	100	NS

Table 4. Neonatal outcomes according to mode of delivery. * PSC = planned caesarean section, † CS after IOL = caesarean section after induction of labor, # NS = not significant. Composite neonatal outcome comprised of: bronchopulmonary dysplasia, retinopathy, intracranial hemorrhage, necrotizing enterocolitis and neonatal seizures

DISCUSSION

The vaginal delivery rate after induction of labor was 1.8-80%. In 0% to 73% of cases a scheduled CD was performed. This large variation might be explained by the small number of patients included as well as different selection criteria. There were no differences described in maternal outcome, nor in neonatal outcomes.

Indications to perform a planned CD were for the most part similar in each of the included studies, such as fetal malpresentation, eclampsia and non-reassuring fetal heart rate patterns. However, other indications, for example favorable cervix, varied between the studies[13,14].

One of the indications for CD after induction of labor was failure to progress. However, analyzing the study of Nassar et al in more detail, the authors state that in 88.2% of the cases the decision to perform a CD was already made in the latent phase of labor which might suggest that some women were not given enough time to enter the active phase of labor[13].

With respect to maternal outcome, two included studies report endometritis and 1 also reports postpartum hemorrhage. These studies showed no difference in maternal outcome between the different groups. A 2013 Cochrane systematic review reviewed all literature on maternal outcome in preterm birth in non-preeclamptic patients, i.e. all deliveries prior to 37 weeks' gestation, without subgroup analysis for different gestational age groups, and compared CD versus vaginal delivery[15]. There was a significant advantage for women in the VD group with respect to maternal puerperal pyrexia (RR 2.98, 95% CI 1.18 to 7.53) and other maternal infections (RR 2.63,95% CI 1.02 to 6.78). There was no significant difference between the VD group and CD group with regard to postpartum hemorrhage (RR 3.69, 95% CI 0.16 to 83.27). As expected, there were significantly more cases of major maternal postpartum complications (wound dehiscence, deep vein

thrombosis, endotoxic shock and puerperal sepsis) in the CD group (RR 7.21, 95% CI1.37 to 38.08). A study by Reddy et al. shows a substantial risk of maternal complications in early preterm birth, such as hemorrhage, infection and ICU admission[16]. This risk is highest for the women undergoing a CD prior to 34 weeks' gestation, depending on which incision is made in the uterus. The risk of a serious maternal complication is 23% with a classical CD versus 3.5% when a woman has a vaginal delivery[16]. Although the aforementioned Cochrane review and the study by Reddy et al. did not specifically include women with preeclampsia, the maternal risks of an early CD may apply to patients with preeclampsia as well. Amorim et al. performed a prospective study on maternal outcome according to delivery amongst patients with preeclampsia and report that CD was associated with increased maternal morbidity, raising the risk of hemorrhagic and infectious complications and the rate of postpartum hypertensive crises and prolonged hospitalization. The mean gestational age in this study was 36 weeks'. The risk of severe maternal complications was 65% higher in women undergoing CD[17].

Two studies in this review report on neonatal outcome according to mode of delivery and find no differences in neonatal outcome according to mode of delivery[10,12]. Recent literature on neonatal outcome at premature gestational ages and mode of delivery in non-preeclamptic patients describes 5055 vertex-presenting singleton pregnancies between 24 and 31 weeks' of gestation[7]. The study revealed no differences in neonatal death, birth asphyxia, or other major newborn morbidities in infants delivered between women who had a CD and those who delivered vaginally. These results are similar to another recent cohort study by Racusin and a study by Običan[18,19]. Both authors conclude that CD does not improve outcome in preterm neonates. However, no distinction is made between preterm appropriate for gestational age (AGA) neonates and preterm small for gestational age (SGA) neonates. Since pregnancies complicated by preeclampsia are frequently complicated by fetal growth restriction, the results of comparison of VD versus CD cannot be extrapolated to women with pregnancies complicated by preeclampsia. Wylie et al studied neonatal outcome in very low-birthweight vertex-presenting preterm AGA infants with SGA infants by mode of delivery[20]. The authors conclude that CD does not improve neonatal survival in the very low birth weight infant.

The study by Običan compares neonatal neurodevelopmental outcome measured by Bayley II scores according to delivery mode in periviable pregnancies. They included 158 neonates born at a gestational age of 22 to 31 weeks. Ninety-one neonates were delivered vaginally and 67 neonates were delivered by CD. They conclude that delivery mode did not impact neurodevelopment as determined by Bayley II scores at 2 years of age. There were no significant differences between groups in both mental (MDI) and physical (PDI) Bayley scores on both raw analysis and after adjusting for potential cofounding variables[19].

Two older studies report a possible neonatal benefit of a VD at gestational ages of 24 to 28 weeks and in very low birth weight infants. Both studies show a lower incidence of respiratory distress syndrome in neonates who were delivered vaginally[21,22].

This review has some limitations. First, the optimal study design to answer the research questions would be a randomized controlled trial. However, randomized controlled trials concerning early onset preeclampsia are not feasible due to the rarity of the condition[7]. Therefore, the included studies represent either prospective - retrospective cohort studies or cross-sectional studies.

Second, the number of included patients per study is small, with a sample size varying from 12 to 56 patients. Third, there is great variation in inclusion- and exclusion criteria between the included studies. There were no studies pertaining to the major maternal outcomes predefined in this review and not all neonatal outcome measures were reported.

CONCLUSION

Studies that do report the success rate of attempted vaginal delivery are limited in size. However, giving the available evidence in the reported studies a trial of labor is a considerable option in counseling women with a pregnancy complicated by preeclampsia prior to 28 weeks' gestation due to the similar maternal and neonatal outcome. Women with a pregnancy complicated by severe onset preeclampsia should be counselled that attempted vaginal delivery has a wide range of success and is not easily predicted. No differences in maternal or neonatal outcome were attributed to the mode of delivery, however, numbers are small.

REFERENCES

1. Abalos E, Cuesta C, Grosso AL et al. Global and regional estimates of preeclampsia and eclampsia: a systematic review. European Journal of Obstetrics & Gynecology and Reproductive Biology 170 (2013) 1–7
2. Lisonkova S, Sabr Y, Mayer C et al. Maternal morbidity associated with early-onset and late-onset preeclampsia. Obstet Gynecol. 2014 Oct;124(4):771-81
3. Roberts D, Brown J, Medley N et al. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2017 Mar 21;3:CD004454.
4. Sibai BM, Barton JR. Expectant management of severe preeclampsia remote from term: patient selection, treatment, and delivery indications. Am J Obstet Gynecol.2007;196:514.e1-514.e9.
5. Alexander JM, Bloom SL, McIntire DD et al. Severe preeclampsia and the very low birth weight infant: is induction of labor harmful? Obstet Gynecol. 1999 Apr;93(4):485-8
6. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. European Journal of Epidemiology 2010, 25 (9):603-605
7. Reddy UM, Zhang J, Sun L, et al. Neonatal mortality by attempted route of delivery in early preterm birth. Am J Obstet Gynecol 2012;207:117.e1-8.
8. Coppage KH and Polzin WJ. Severe preeclampsia and delivery outcomes: Is immediate cesarean delivery beneficial? Am J Obstet Gynecol 2002;186:921-3
9. Hall DR , Odendaal HJ, Steyn DW. Delivery of patients with early onset, severe pre-eclampsia. Int J Gynaecol Obstet. 2001 Aug;74(2):143-50
10. Alanis MC, Robinson CJ, Hulsey TC et al. Early-onset severe preeclampsia: induction of labor vs elective cesarean delivery and neonatal outcomes. Am J Obstet Gynecol 2008;199:262.e1-262.e6
11. Mashiloane CD, Moodley J. Induction or caesarean section for preterm pre-eclampsia. J Obstet Gynecol 2002;22:4.353-356
12. Blackwell SC, Redman ME, Tomlinson M et al. Labor induction for the preterm severe preeclamptic patient: is it worth the effort? J Matern Fetal Neonatal Med 2001;10;305-311
13. Nassar AH, Adra AM, Chakhtoura N et al. Severe preeclampsia remote from term: Labor induction or elective cesarean delivery? Am J Obstet Gynecol 2001;179:5.1210-1213
14. Kim LH, Cheng YW, Delaney S. Is preeclampsia associated with an increased risk of cesarean delivery if labor is induced? J Matern Fetal Neonatal Med 2010;23(5): 383-388
15. Alfirevic Z, Milan SJ, Livio S. Caesarean section versus vaginal delivery for preterm birth in singletons (Review). Cochrane Database Syst Rev. 2013 Sep 12;(9):CD000078
16. Reddy UM, Rice MM, Grobman WA et al. Serious maternal complications after early preterm delivery (24–33 weeks' gestation). Am J Obstet Gynecol 2015;213(October (4)):538.e1–9
17. Amorim MM, Katz L, Barros AS et al. Maternal outcomes according to mode of delivery in women with severe preeclampsia: a cohort study. J Matern Fetal Neonatal Med. 2015 Apr;28(6):654-60
18. Racusin DA, Antony KM, Haase J et al. Mode of Delivery in Premature Neonates: Does It Matter? AJP Rep. 2016 Jul;6(3):e251-9
19. Običan SG, Small A, Smith D et al. Mode of delivery at periviability and early childhood neurodevelopment. Am J Obstet Gynecol 2015;213:578.e1-4
20. Wylie BJ, Davidson LL, Batra M et al. Method of delivery and neonatal outcome in very low-birthweight vertex-presenting fetuses. Am J Obstet Gynecol 2008;198:640.e1-640.e7
21. Regenstein AC, Laros RK Jr, Wakeley A et al. Mode of delivery in pregnancies complicated by preeclampsia with very low birth weight infants. J Perinatol. 1995 Jan-Feb;15(1):2-6
22. Kitchen W, Ford GW, Doyle LW et al. Cesarean section or vaginal delivery at 24 to 28 weeks' gestation: comparison of survival and neonatal and two-year morbidity. Obstet Gynecol. 1985 Aug;66(2):149-57

SUPPLEMENTARY INFORMATION

A review protocol was developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)-statement (www.prisma-statement.org). A comprehensive search was performed in the bibliographic databases PubMed, Embase.com and Wiley Cochrane Library from inception up to June 2nd 2017, in collaboration with a medical librarian (see tables 1-3).

#	Query	Results
#5	#1 AND #2 AND #3 AND #4	789
#4	"Delivery, Obstetric"[Mesh:noexp] OR "Cesarean Section"[Mesh] OR cesarea*[tiab] OR caesarea*[tiab] OR "c section"[tiab] OR "c sections"[tiab] OR (vaginal[tiab] AND (birth[tiab] OR delivery[tiab] OR parturition[tiab])) OR mode of delivery[tiab] OR modus of delivery[tiab]	92,473
#3	"Pregnancy Outcome"[Mesh] OR ((maternal[tiab] OR neonatal[tiab] OR neonatal[tiab]) AND outcome*[tiab])	93,354
#2	time of delivery[tiab] OR early[tiab] OR precocious[tiab] OR severe[tiab]	1,955,521
#1	"Hypertension, Pregnancy-Induced"[Mesh] OR preeclamp*[tiab] OR eclamp*[tiab] OR toxemi*[tiab] OR hellp[tiab]	43,494

PubMed Session Results (02 Jun 2017)

#	Query	Results
#5	#1 AND #2 AND #3 AND #4	1,460
#4	'delivery'/de OR 'cesarean section'/exp OR cesarea*:ab,ti OR caesarea*:ab,ti OR 'c section':ab,ti OR 'c sections':ab,ti OR (vaginal:ab,ti AND (birth:ab,ti OR delivery:ab,ti OR parturition:ab,ti)) OR 'mode of delivery':ab,ti OR 'modus of delivery':ab,ti	143,827
#3	'pregnancy outcome'/exp OR ((maternal:ab,ti OR neonatal:ab,ti OR 'neo-natal':ab,ti) AND outcome*:ab,ti)	108,931
#2	'time of delivery':ab,ti OR early:ab,ti OR precocious:ab,ti OR severe:ab,ti	2,602,274
#1	'maternal hypertension'/exp OR preeclamp*:ab,ti OR eclamp*:ab,ti OR toxemi*:ab,ti OR hellp:ab,ti	54,627

Embase.com Session Results (02 Jun 2017)

#	Query	Results
#5	#1 and #2 and #3 and #4	135
#4	("obstetric delivery" OR "cesarean section" OR cesarea* OR caesarea* OR "c section" OR "c sections" OR (vaginal AND (birth OR delivery OR parturition)) OR "mode of delivery" OR "modus of delivery"):ab,ti,kw	9,952
#3	("pregnancy outcome" OR ((maternal OR neonatal OR "neo-natal") AND outcome*)):ab,ti,kw	12,258
#2	("time of delivery" OR early OR precocious OR severe):ab,ti,kw	128,098
#1	("pregnancy-induced hypertension" OR "maternal hypertension" OR preeclamp* OR eclamp* OR toxemi* OR help):ab,ti,kw	21,939

Wiley / Cochrane Library Session Results (02 Jun 2017)
135 items (35 Cochrane Reviews ; 100 Trials)

Quality assessment criteria	Acceptable(*)	Reddy	Alanis	Mashiloane	Coppage	Blackwell	Hall	Nassar	Kim
Selection									
Representativeness of exposed cohort?	Representative of average women with early preeclampsia	*	*	*	*	*	*	*	*
Selection of the non-exposed cohort?	Drawn from same community as exposed cohort	*	*	*	*	*	*	*	*
Ascertainment of exposure?	Secured records, Structured interview	*	*	*	*	*	*	*	*
Demonstration that outcome of interest was not present at start of study?	Yes	*	*	*	*	*	-	*	*
Comparibility									
Study controls for gestational age?	Yes	*	*	*	-	*	*	*	-
Study controls for at least 3 additional risk factors?	Yes	*	*	*	*	*	*	*	*
Outcome									
Assessment of outcome?	Independent blind assessment, record linkage	*	*	*	*	*	*	*	*
Was follow-up long enough for outcome to occur?	Yes	*	*	-	-	*	-	-	-
Adequacy of follow-up of cohorts?	Complete follow-up, or subjects lost to follow-up unlikely to introduce bias	-	-	-	-	-	-	-	-
Overall Quality Score (Maximum = 9)		**8**	**8**	**7**	**6**	**8**	**6**	**7**	**6**

Supplemental Table 4. Newcastle-Ottawa scale for assessment of quality of included studies – Cohort studies (each asterisk represents if individual criterion within the subsection was fulfilled)

Chapter 8

Modelprotocol

‘Medisch handelen bij beëindigen van de zwangerschap op maternale indicatie’

L. van Eerden, E. Pajkrt, A.C. Bolte, C.J.M. de Groot,
G.C.L.M. Page-Christitaens, G.G. Zeeman, T.P. Schaap

www.nvog.nl/kwaliteitsdocumenten/protocollen

DEFINITIE

"Beëindigen van de zwangerschap met als doel het leven en/of de gezondheid van moeder te beschermen, waarbij de kans op neonatale overleving dusdanig klein wordt geacht dat er geen interventies worden gedaan op foetale indicatie, ongeacht de zwangerschapsduur."

1. INLEIDING

Enkele keren per jaar ontstaat er in of door de zwangerschap een dermate gevaarlijke situatie voor de moeder, dat er een reden is om de zwangerschap voortijdig te beëindigen op maternale indicatie om ernstige morbiditeit te reduceren of maternale sterfte te voorkomen[1].

Men spreekt van het beëindigen van de zwangerschap op maternale indicatie indien besloten is tot beëindiging van de zwangerschap, met als doel het leven en/of de gezondheid van moeder te beschermen, waarbij er geen interventies worden gedaan op foetale indicatie, ongeacht de zwangerschapsduur. Interventies op foetale indicatie worden achterwege gelaten omdat de prognose van de ongeboren vrucht (door bijvoorbeeld termijn en/of foetale conditie) als ongunstig wordt veronderstelt. Dit terwijl de mogelijke maternale nadelen van een op foetale overleving gerichte interventie deze interventie niet rechtvaardigt. De maternale indicaties kunnen zowel een direct gevolg zijn van de zwangerschap (bijv. ernstige pre-eclampsie of levensbedreigend bloedverlies bij een placenta praevia) of indirect (bijv. ernstige ARDS (Acute respiratory distress syndrome) ten gevolge van sepsis). In beide gevallen kan worden besloten dat het continueren van de zwangerschap kan leiden tot ernstige schade bij de moeder, of zelfs levensbedreigend kan zijn.

Volgens de gehanteerde definitie is er **geen** sprake van het beëindigen van een zwangerschap op maternale indicatie, indien er een beëindiging van de zwangerschap plaats vindt op maternale indicatie waarbij er tevens wordt gestreefd naar een optimale foetale uitkomst (lees: inleiding bij ernstige pre-eclampsie waarbij zo nodig wel op foetale indicatie wordt geïntervenieerd).

Het wel of niet overlijden is niet relevant voor de gehanteerde definitie van een zwangerschapsbeëindiging op maternale indicatie. Deze gekozen definitie waarborgt hiermee ook de registratie van beëindigingen na 24 weken waarbij de foetus daadwerkelijk komt te overlijden.

Dit modelprotocol beschrijft de gedragscode hoe een arts dient te handelen in geval van een ernstige aandoening van de moeder, indien wordt overwogen de zwangerschap te beëindigen om ernstige morbiditeit te reduceren of maternale sterfte te voorkomen

en er geen interventie wordt gedaan op foetale indicatie. Het beschrijft tevens de procedures van de voorbereidingen, de afbreking en de melding bij NethOSS (Netherlands Obstetric Surveillance System) (zie 'Registratieprotocol NethOSS').

2. HET PROTOCOL

2.1. Algemeen

Het beëindigen van de zwangerschap op maternale indicatie zal in principe plaats vinden in één van de tien derdelijns perinatologische centra in Nederland, die beschikken over een maternale high care unit en een neonatale intensive care unit (NICU).

Er zijn uitzonderingen waarbij overwogen kan worden om de zwangerschap te beëindigen in de 2e lijn, waarbij overleg met een derdelijns perinatologisch centrum uiteraard wel is geïndiceerd:

- gevallen waarbij er een dusdanige spoedsituatie bestaat waarbij de inschatting is dat overplaatsing naar een derdelijns centrum niet meer mogelijk is (bijvoorbeeld massaal bloedverlies bij een placenta praevia).

Artsen die betrokken zijn bij de procedure rond zwangerschapsbeëindiging zijn ieder voor zich verantwoordelijk voor het eigen medisch handelen. Er wordt vastgelegd welke arts eindverantwoordelijk is. Een beëindiging van de zwangerschap op maternale indicatie is niet strafbaar op grond van artikel 82a van het Wetboek van Strafrecht, omdat potentieel het leven van de moeder in gevaar is[2]. Wellicht ten overvloede hoeft een termijn van 5 dagen bedenktijd in deze situatie niet te worden aangehouden.

2.2. De diagnose

Alle levensbedreigende aandoeningen van de moeder, waarbij er naar heersend medisch inzicht geen redelijke twijfel bestaat over de diagnose en waarbij het beëindigen van de zwangerschap als doel heeft ernstige maternale morbiditeit te reduceren en mortaliteit te voorkomen, kunnen in aanmerking komen voor een zwangerschapsbeëindiging. De volgende maternale indicaties zijn beschreven in recent onderzoek naar zwangerschapsbeëindigingen in Nederland, welke in het verleden hebben plaatsgevonden[3]. De lijst hieronder is niet limitatief:

- Hypertensieve aandoeningen in de zwangerschap: ruim 2/3 van de zwangerschapsbeëindigingen op maternale indicatie betreft zwangere vrouwen met ernstige vroege pre-eclampsie. Er is consensus in de internationale literatuur dat bij vrouwen die vóór 24 weken zwangerschapsduur ernstige pre-eclampsie ontwikkelen, zwangerschapsbeëindiging overwogen moet worden[4-5]. Argumenten hiervoor zijn dat een afwachtend beleid grote risico's voor de moeder met zich mee brengt, terwijl de

overlevingskansen voor de foetus klein en de kans op ernstige neonatale morbiditeit groot wordt geschat, met name in het geval van een ernstige foetale groeirestrictie. Na 24 weken zwangerschapsduur wordt zo mogelijk individueel beleid gemaakt, waarbij de risico's voor de moeder moeten worden afgewogen tegen de kansen voor het kind. Bij die afweging wordt de prognose voor overleving van de foetus meegenomen.

- Sepsis of Systemic Inflammatory Respons Syndrome bij extreem preterm (< 24 weken) gebroken vliezen.
- Ernstige exacerbatie van auto-immuunziekten.
- Ernstige verslechtering van de cardiale functie bij cardiale aandoeningen.
- Afstoten van een transplantatie orgaan.
- Levensbedreigende obstetrische bloedingen.
- Maligniteit bij de moeder. Een maligniteit in de zwangerschap zal slechts af en toe aanleiding zijn tot het afbreken van de zwangerschap, omdat in het algemeen de meeste oncologische behandelingen kunnen plaatsvinden bij een intacte zwangerschap. Er kan een advies worden gevraagd aan de landelijke adviesgroep Kanker en Zwangerschap (www.iknl.nl).

2.3. De prognose

De aard en de ernst van de aandoening(en) worden zo zorgvuldig mogelijk omschreven, alsmede de prognose voor de latere gezondheidstoestand van de moeder. Ook eventuele bijkomende foetale verschijnselen die het gevolg zijn van de zwangerschap en/of van de aandoening van de moeder (ernstige groeirestrictie, hoeveelheid vruchtwater enz.) worden nauwkeurig gedocumenteerd. Naar op dat moment heersend medisch inzicht, wordt het niet zinvol geacht foetale bewaking toe te passen of te interveniëren op foetale indicatie. Deze interventies op foetale indicatie worden achterwege gelaten omdat de prognose van de ongeboren vrucht als dermate ongunstig wordt verondersteld of omdat de mogelijke gezondheidsrisico's van deze interventie voor de moeder deze interventie niet rechtvaardigt. In principe wordt er geen foetale bewaking toegepast tijdens een bevalling.

2.4. De wens van de ouders

Er wordt zorgvuldig zorg gedragen voor begrijpelijke en volledige voorlichting aan de ouders over de aard en de prognose van de aandoening van de moeder en de te verwachten zeer slechte tot infauste prognose voor het kind. Er wordt altijd, naar het geldende inzicht op dat moment, besproken met de ouders of het verlengen van de zwangerschap tot de mogelijkheden behoort. Er worden mogelijkheden aangereikt voor steun door bijvoorbeeld een maatschappelijk werkende, geestelijk verzorger of patiëntenorganisatie(s). In voorkomende gevallen is er geen overleg met de vrouw mo-

gelijk (bijvoorbeeld bij een gesedeerde en geïntubeerde patiënte). Het gesprek zal dan primair plaatsvinden met de partner, of indien niet aanwezig, familie van de patiënte. De KNMG (Koninklijke Nederlandse Maatschappij ter bevordering van Geneeskunde) adviseert dat indien er sprake is van een noodsituatie en toestemming van de patiënt of diens vertegenwoordiger ontbreekt, te handelen in overeenstemming met de professionele standaard[6].

2.5. De besluitvorming

De besluitvorming voor het beëindigen van een zwangerschap op maternale indicatie dient plaats te vinden in een overlegteam.

2.5.1. Samenstelling van het overlegteam

Indien de klinische situatie van de moeder dit toelaat, wordt iedere casus met het verzoek tot beëindiging van de zwangerschap op maternale indicatie besproken in een multidisciplinair teamoverleg waarin minimaal twee gynaecologen (waarvan één als niet-behandelaar), een kinderarts (die zijn afdeling vertegenwoordigt) en zo nodig een deelspecialist (bijvoorbeeld intensivist, cardioloog) zitting hebben. In voorkomende gevallen kan er ook overleg plaatsvinden met collega's uit andere, (inter)nationale, instellingen met specifieke expertise. Met het oog op de eigen professionele inbreng en het contact met de zwangere kunnen ook een klinisch verloskundige, verpleegkundige en maatschappelijk werkende een adviesfunctie hebben voor het overlegteam. In spoedsituaties (bijvoorbeeld bij een bloedende placenta praevia of in een reanimatie setting) kan besloten worden om geen overleg te voeren. De handelingen dienen wel na de bevalling zorgvuldig beargumenteerd en vastgelegd te worden.

2.5.2. Taak van het overlegteam

Het overlegteam dient na te gaan of:

- het beëindigen van de zwangerschap gerechtvaardigd is op basis van de ernst van de aandoening(en) en er naar heersend medisch inzicht geen redelijke twijfel bestaat over de diagnose en prognose;
- de ouders in voldoende mate zijn voorgelicht over de aard en de ernst van de aandoening en de prognose en of deze informatie door de ouders is begrepen;
- er overeenstemming is binnen het perinatologisch team (bestaande uit gynaecologen, neonatologen en andere betrokken medisch specialisten) over het postnatale beleid in geval van een beëindiging van de zwangerschap na 24 weken en er onverwacht toch een levend kind wordt geboren;
- het medisch hoofd, c.q. het plaatsvervangend hoofd van de afdeling geïnformeerd is over de voorgenomen zwangerschapsbeëindiging.

Het wordt geadviseerd het beëindigen van de zwangerschap voorbij 24 weken ook te melden aan de Raad van Bestuur van de instelling. De uitkomst van de bespreking van het overlegteam dient gedocumenteerd te worden in het medisch dossier van de moeder.

2.5.3. Overleg met de ouders

De behandelend gynaecoloog bespreekt zo spoedig mogelijk het resultaat van de besluitvorming met de ouders. De gang van zaken voor en na de geboorte wordt uiteengezet wanneer tot het beëindigen van de zwangerschap is besloten.

De behandelend gynaecoloog overtuigt zich er persoonlijk van of de informatie duidelijk en volledig is overgekomen. Indien de toestand van de moeder dit toelaat, krijgen de ouders de tijd om de informatie op zich in te laten werken en in eigen kring te bespreken. De behandelend gynaecoloog wijst de ouders op de mogelijkheid om gesprekken te voeren met een maatschappelijk werkende, een geestelijk verzorger en/of een vertrouwenspersoon die zij zelf uitkiezen. Nadat de beslissing tot zwangerschapsbeëindiging is genomen, informeert de behandelend gynaecoloog de huisarts, de verloskundige en de verwijzend specialist, tenzij de ouders daartegen bezwaar maken. In voorkomende gevallen is er geen overleg met de vrouw mogelijk (bijvoorbeeld bij een gesedeerde en geïntubeerde patiënte). Het gesprek zal dan primair plaatsvinden met de partner, of indien niet aanwezig, familie van de patiënte (zie ook paragraaf 2.4).

2.6. De uitvoering

2.6.1. Voorbereiding

In overleg met de behandelend arts en eventueel deelspecialist wordt de meest veilige plaats voor de partus bepaald. Dit kan zijn op het verloskamercomplex, maar ook op een high care afdeling, hartbewaking- of intensive care afdeling.

2.6.2. Methode

Er wordt gekozen voor de meest veilige methode voor de moeder, gegeven de medische problematiek. De ouders worden voorbereid op het feit dat na 22 weken het kind nog met enige levenstekenen kan worden geboren, met name indien er sprake is van een sectio (bijvoorbeeld bij een bloedende placenta praevia). Tijdens de uitvoering wordt de uiterste zorg besteed aan continuïteit van zorg en aan de begeleiding van de ouders, waarbij de gynaecoloog te allen tijde de eindverantwoordelijkheid draagt voor wat betreft het medisch inhoudelijke beleid als wel de begeleiding van de ouders.

2.7. Na de bevalling

Ouders dienen in staat te worden gesteld om op passende wijze afscheid te nemen. Afhankelijk van de aard en de ernst van de maternale aandoening wordt het beleid voor de moeder verder bepaald.

2.8. Informatie aan derden

2.8.1. Wetgeving

Indien de bevalling plaatsvindt **voor** 24 weken zwangerschapsduur hoeft er geen melding gedaan te worden bij de forensisch arts (voorheen gemeentelijk lijkschouwer genoemd). Tevens hoeft er geen aangifte van geboorte te worden gedaan, maar in de meeste gemeenten is dit wel mogelijk indien de ouders dat wensen[7].

Indien de bevalling plaatsvindt **na** 24 weken en de vrucht is komen te overlijden, dient de forensisch arts altijd te worden geïnformeerd door de betrokken gynaecoloog. Er kan overwogen worden een voormelding te doen op het moment dat besloten is tot het beëindigen van de zwangerschap na 24 weken. Een verklaring van geen bezwaar van de officier van justitie is noodzakelijk voordat tot lijkbezorging kan worden overgegaan. Tevens dient er bij een geboorte na 24 weken aangifte van de geboorte te worden gedaan in de gemeente waar de bevalling heeft plaatsgevonden[7].

2.8.2 Overige informatie aan derden

De betrokken hulpverleners (gynaecoloog, verloskundige, huisarts, maatschappelijk werkende) worden zo spoedig mogelijk na de zwangerschapsbeëindiging geïnformeerd, tenzij de ouders daartegen bezwaar maken.

2.9. Nazorg

Met de ouders wordt overlegd over de begrafenis c.q. crematie. Voor de begeleiding en nazorg wordt in het ziekenhuis en in de thuissituatie zorggedragen. Afhankelijk van de situatie kan deze nazorg verleend worden door bijvoorbeeld de behandelend gynaecoloog, de huisarts, de verloskundige, de geestelijk verzorger en/of de maatschappelijk werkende. De behandelend gynaecoloog biedt de ouders een aantal weken na de zwangerschapsbeëindiging een gesprek aan waarin het gehele proces wordt besproken en waarin aandacht besteed wordt aan de rouwverwerking. De ouders worden verder geïnformeerd over de diagnose, het herhalingsrisico en de mogelijkheden van primaire preventie in een eventuele toekomstige zwangerschap.

2.10. Verslaglegging

In het medisch dossier worden nauwkeurig, gedateerd en chronologisch de volgende gegevens vastgelegd:

- de persoonsgegevens van de zwangere;
- de gegevens betreffende de zwangerschap;
- de gegevens betreffende de diagnose en de prognose;
- een weergave van de gesprekken met de ouders na het stellen van de diagnose en de prognose en van de gevoerde nagesprekken;
- de samenstelling van het overlegteam;

- een weergave van de besluitvorming tijdens het teamoverleg;
- het voorgestelde beleid als het kind levend wordt geboren;
- verslag van een eventuele consultatie vooraf;
- een weergave van het gesprek met de ouders na het teamoverleg;
- het verloop van de inleiding, bevalling en uitwendige schouwing;
- de melding aan de forensisch arts (voorheen gemeentelijk lijkschouwer);
- de geboden nazorg aan de ouders;
- de evaluatie door betrokkenen;
- de namen van al diegenen die bij de procedure betrokken zijn geweest;
- de arts die eindverantwoordelijk is.

De eindverantwoordelijke gynaecoloog draagt zorg voor melding en verslag conform de daaraan te stellen eisen (zie hoofdstuk 3, Registratie).

3. REGISTRATIE DOOR NETHOSS TEN BEHOEVE VAN HET BIJHOUDEN VAN EEN LANDELIJKE REGISTRATIE (ZIE 'REGISTRATIEPROTOCOL NETHOSS')

3.1. Inleiding

Per 1 februari 2016 is de nieuwe 'Regeling beoordelingscommissie late zwangerschap beëindiging en levensbeëindiging bij pasgeborenen' in werking getreden. In de toelichting staat expliciet vermeld dat zwangerschappen die beëindigd worden op maternale indicatie niet gemeld hoeven te worden.

Anders dan bij late zwangerschapsbeëindiging categorie 1- en 2-gevallen[1] is het doel van de behandeling het beschermen van het leven en/of de gezondheid van de moeder in plaats van het laten overlijden van de ongeboren vrucht. Hoewel de zwangerschapsbeëindiging bij een maternale indicatie niet is gericht op het laten overlijden van de vrucht, is de (juridische) consequentie bij het overlijden van de vrucht naar aanleiding van het beëindigen van de zwangerschap een niet-natuurlijke dood. In die gevallen is artikel 82a van het Wetboek van Strafrecht (Sr) van toepassing – evenals 296 Sr2. Het betreft een niet-natuurlijk overlijden waarbij naar de letter van de wet sprake is van een strafbaar feit[2]. Beëindiging van de zwangerschap na 24 weken zwangerschapsduur als noodzakelijke en enige mogelijke behandeling van een ernstige aandoening bij de moeder behoort echter tot aanvaardbaar en adequaat, onvermijdbaar medisch handelen. Zulk handelen zal in de regel vallen onder de strafuitsluitingsgrond noodtoestand, waardoor de strafbaarheid van het handelen komt te ontvallen. Er is geen noodzaak deze gevallen te laten beoordelen in het kader van zwangerschapsbeëindiging die samenhangt met de toestand van het kind en deze gevallen hoeven dus niet te worden gemeld bij de beoordelingscommissie. Wel dient, in het geval de vrucht komt te

overlijden, zoals bij elk overlijden, dit gemeld te worden bij de forensisch arts (voorheen gemeentelijk lijkschouwer). Bovendien heeft de Inspectie voor de Gezondheidszorg in deze een toezichthoudende taak. Mocht de met het toezicht belaste ambtenaar een ernstige schending van de professionele standaard constateren dan kan hij daarvan melding of aangifte doen bij het Openbaar Ministerie. Alleen in dat geval, en in het geval dat de officier van justitie via een andere weg een aangifte of melding ontvangt, heeft het Openbaar Ministerie een rol. In alle andere gevallen van late zwangerschapsbeëindiging op maternale indicatie beperkt de rol van de officier van justitie zich tot een beoordeling van het verlof tot begraven of cremeren.

Bij het tot stand komen van deze nieuwe regeling is met het Ministerie van VWS (Volksgezondheid, Welzijn en Sport) afgesproken dat de beroepsgroep zelf zorg zal dragen voor een adequate registratie en analyse van zwangerschapsbeëindiging op maternale indicatie na 24 weken. Het doel van deze registratie is het verkrijgen van inzicht in indicaties en gevolgde procedures. De analyses worden nadrukkelijk niet gebruikt voor juridische doeleinden. Vanuit wetenschappelijk oogpunt en gelet op de kwaliteit van zorg is het belangrijk alle zwangerschappen die worden beëindigd op maternale indicatie te analyseren, ongeacht of er sprake was van een zwangerschapsduur na 24 weken. Door de NVOG (Nederlandse Vereniging voor Obstetrie & Gynaecologie) is besloten dat de registratie zal verlopen via NethOSS (Netherlands Obstetric Surveillance System): Registratie 'Zwangerschapsbeëindiging op Maternale Indicatie (ZMI)'.

3.2. Procedure

Alle casus (zowel in de tweede als derde lijn) van zwangerschapsbeëindiging op maternale indicatie dienen te worden gemeld bij de NethOSS. De NethOSS valt onder de Auditcommissie Maternale Sterfte en Morbiditeit (AMSM) van de NVOG. Bij de totstandkoming van de nieuwe Regeling is afgesproken dat de beroepsgroep zelf zorg zal dragen voor een adequate registratie en analyse van late zwangerschapsbeëindiging op maternale indicatie. Het doel van deze registratie is het verkrijgen van inzicht in indicaties, gevolgde procedures en het vaststellen van eventuele regionale verschillen ongeachte de zwangerschapsduur. De analyses worden nadrukkelijk niet gebruikt voor juridische doeleinden.

De casus zullen worden achterhaald door gebruik te maken van het NethOSS-netwerk van de AMSM. Om zeker te zijn dat alle casus worden geregistreerd zal via de maandelijkse mail aan één verantwoordelijk gynaecoloog van ieder ziekenhuis met een verloskunde afdeling worden gevraagd of er een zwangerschapsbeëindiging op maternale indicatie is geweest.

REFERENTIES

1. Modelprotocol: Medisch Handelen Late Zwangerschapsafbreking, versie 3.0, NVOG, 12 december 2017
2. www.wetboek-online.nl/Sr82a
3. Van Eerden L, Zeeman GG, Page-Christiaens, GCM, et al. Termination of pregnancy for maternal indications at the limits of fetal viability: a retrospective cohort study in the Dutch tertiary care centres. BMJ Open 2014;4:e005145. doi:10.1136/bmjopen-2014-005145
4. Sibai BM, Barton JR. Expectant management of severe preeclampsia remote from term: patient selection, treatment, and delivery indications. AM J Obstet Gynecol 2007;196:514.e1-9
5. NICE guideline Hypertension in Pregnancy August 2010. Available at: www.nice.org.uk/guidance/CG107
6. Van wet naar praktijk. Implementatie van de WGBO. Deel 2 Informatie en toestemming. KNMG 2004
7. Wet op de Lijkbezorging. www.wetboek-online.nl

Chapter 9

General discussion
and future perspectives

During pregnancy the health of both the mother as well as the fetus can be severely compromised by several conditions, either those limited to pregnancy, such as pre-eclampsia, or co-existing conditions that emerge or worsen during pregnancy. In some cases the threat to maternal health and life becomes so severe, that the primary question arises whether or not the pregnancy needs to end immediately[1]. When that is indeed the case, at a gestational age where fetal viability is still limited, a decision pertaining to active fetal management has to be made, based on estimation of fetal viability. Two possible management options become apparent in cases where the gestational age is at the limits of fetal viability:

1. termination of pregnancy without intention to intervene for fetal indications and without active neonatal support
2. termination of pregnancy with the explicit intention to intervene for fetal indications and active neonatal management.

This thesis is focused on the complex process of decision making in cases where maternal reasons dictate that the pregnancy needs to end while the gestational age has only progressed to the period where there is still serious concern about fetal viability. We found that once the decision is made that the pregnancy has to end, in the Netherlands, termination of pregnancy for maternal indications occurs approximately 18 times per year, mostly for hypertensive disorders in pregnancy. This number has slightly decreased over time due to changing guidelines on the earliest gestational age and the estimated fetal weight for active neonatal management. Pregnancy outcome in women following termination of pregnancy for hypertensive disorders is uneventful in 53%. The recurrence rate of preeclampsia is 29-31%. Furthermore we found that professionals involved are willing to report cases of termination of pregnancy for maternal indications, with the purpose of performing internal audits.

For the second management option, that is with the explicit intention to intervene for fetal indications and active neonatal management, we found that, in the Netherlands, when preeclampsia occurs prior to 26 weeks' gestation, maternal complications occurred frequently (50%) and neonatal survival was limited (19%). For the optimal delivery mode in severe early onset preeclampsia we found that a trial of labor is a considerable option in counseling women with a pregnancy complicated by preeclampsia prior to 28 weeks' gestation due to the similar maternal and neonatal outcome. These data will be discussed in detail below.

To be able to provide accurate counseling and reduced unwanted practice variation in these difficult cases teams of obstetricians and neonatologists need to incorporate contemporary scientific data and expert consensus. Therefore, outcome of the questions raised in this thesis was employed to develop a Dutch guideline describing the

necessary medical care and considerations in cases where termination of pregnancy for maternal indications at the limits of fetal viability is considered.

Part I: Termination of pregnancy for maternal indications without intention to intervene for fetal indications and without active neonatal support

Incidence

Literature on termination of pregnancy for maternal indications at the limits of fetal viability is scarce. In the Netherlands such cases are generally referred to one of 10 tertiary obstetric care centers. The retrospective Dutch cohort study described in this thesis (chapter 2) demonstrates an overall yearly incidence of approximately 18 cases. In the majority of these cases termination of pregnancy is performed for hypertensive disorders (74%). Other indications include maternal sepsis in the presence of preterm, prelabor rupture of membranes, worsening of pre-existing cardiac conditions, worsening of pre-existing autoimmune disorders, maternal malignancies and severe obstetric bleeding.

Practice variation

There appears to be quite some variation in the number of such terminations between the 10 Dutch tertiary care centers (figure 1).

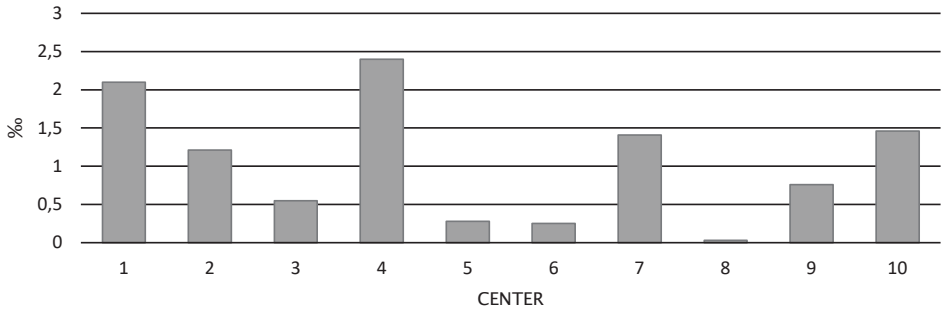


Figure 1. Number of terminations of pregnancy per tertiary obstetric care center per 10 years (in ‰)

This may, amongst others, be due to different local interpretation and counseling on when to embark on active neonatal management at the limits of viability during the past decade when thresholds for active management have been subject to gradual change globally as well as nationally. In the Netherlands, prior to 2006, the overall limit for active obstetric and neonatal management was 26 weeks' of gestation. After 2006 the recommended limit was 25 weeks' gestation, with an estimated fetal weight of at least 500 grams. In the latest Dutch guideline dating September 2010 the recommended limit is 24 weeks' gestation for intubation and ventilation and 25 weeks for cardiac resuscitation. Estimated fetal weight limits are no longer included[2]. A Dutch study on

perinatal practice at the limits of viability shows a wide variety concerning individually preferred treatment decisions[3]. The professional views varied most at 24 and 25 weeks', with a wide range in perceived lowest limits of gestational age for interventions such as a cesarean section and whether or not a neonatologist was present at birth for immediate evaluation of the viability and subsequent initiation of resuscitative measures of the neonate[3]. Another explanation for the practice variation might be differences in incidence of severe early onset preeclampsia as well as the size and/or socioeconomic differences pertaining to the referral population in the regions of these centers. Dutch studies show marked differences in maternal mortality and perinatal mortality between cities, provinces and neighbourhoods[4]. The Maternal Mortality Rate (MMR) in the four largest Dutch cities is significantly higher than the overall MMR in The Netherlands. A possible explanation could be that urbanisation is associated with an increase in environmental health risks, stress, and low socio-economic status[5].

Management

In the subgroup of women with early-onset hypertensive disorders, between 2000 and 2014, the mean gestational age at admission was $23^{5/7}$ weeks ± 9 days. Over the last decades, experts in the field as well as the WHO guideline state that, due to the high maternal morbidity rate and the absence of obvious perinatal benefits associated with expectant management[6-8], a woman who develops preeclampsia prior to a gestational age of 23-24 weeks' should be counseled towards termination of pregnancy. Despite this global consensus, in 75% of the cases described in this thesis, expectant management was initially recommended, with a mean interval between admission and start of termination of 9 days ± 5 days. In this group 75% of women experienced severe complications (HELLP syndrome, seizures or ICU admission). Expectant management did not improve fetal outcome, since all pregnancies were eventually terminated without intention to intervene for fetal indications and without active neonatal support. As described before, during this study (2000-2014) the latest version of the national guideline on perinatal management in case of extreme premature birth was introduced (2010). There appears to be an effect, as expected, on the number of terminations of pregnancy for maternal indications without intention to intervene for fetal indications and without active neonatal support per year (figure 2).

Fetal viability

In this thesis it was found that in order to come to the conclusion that termination of pregnancy is an option to be offered, the following parameters were taken into consideration: gestational age at time of the decision, estimated fetal weight (EFW), growth restriction, lack of interval growth and Doppler profiles. It is known that gestational age is the major factor contributing to fetal viability. Contemporaneous statistics show that

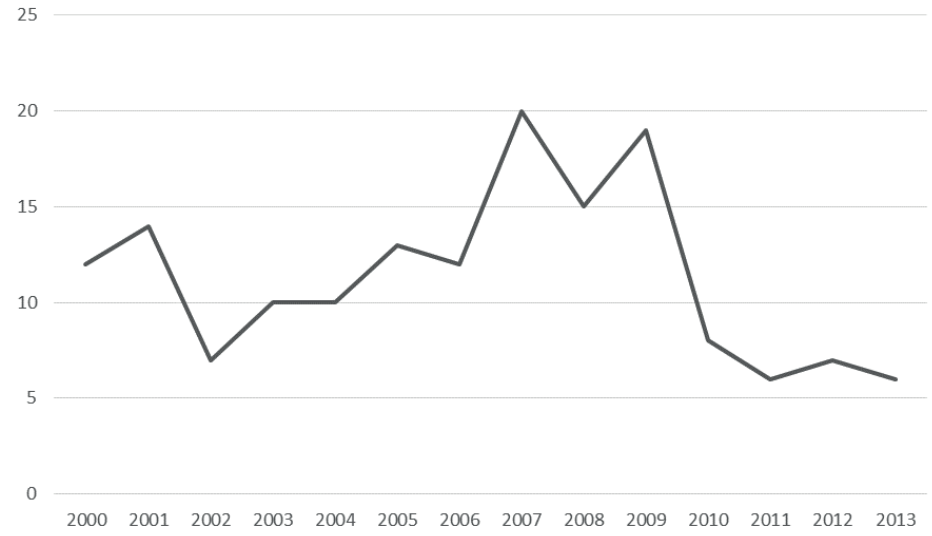


Figure 2. The number of terminations of pregnancy for maternal indications without intention to intervene for fetal indications and without active neonatal support per year

survival rates rise between 22 and 25 weeks' gestation from 6-37% at 22 weeks' gestation to 59-86% at 25 weeks' gestation[9-11]. Another prognostic factor for fetal viability is ultrasound estimated fetal weight. A retrospective study shows that determining EFW in extreme preterm and small for gestational age (SGA) fetuses is less accurate compared to appropriate for gestational age (AGA) fetuses and that EFW is more likely to be overestimated[12]. Furthermore, the risk for fetal death in SGA fetuses is twice the rate of AGA fetuses, especially if the estimated fetal weight is less than the fifth percentile for gestational age[13-14]. In 1/3 of the cases described in this thesis more than 10% under-, or overestimation of EFW was described as compared to the actual birth weight.

Counseling

As shown in this thesis (chapter 5) opinions on whether or not to start active neonatal support may vary but should be a joint effort of obstetricians, neonatologists and the parents alike[15]. Disagreement between perinatal professionals in or between perinatal centers on management decisions in extremely preterm gestations could potentially lead to a conflict in perinatal care[16]. Therefore, it is obvious that counseling on pregnancy and neonatal management at the limits of fetal viability should be a very concise multidisciplinary effort, to ascertain that the final decision is in the best interest of both mother and child and their families.

Legal aspects of termination of pregnancy at the limits of fetal viability

International perspective

Globally, there are significant differences in legislation pertaining to termination of pregnancy. Even though in most countries termination of pregnancy is allowed when the mother's life is in danger, there are also countries were this is not allowed, such as in Thailand or many Latin-American countries[17]. This topic remains highly relevant for each and every society.

National perspective

In the Netherlands termination of pregnancy is allowed up to the gestational age when a newborn can survive outside the womb. This is currently considered $24^{0/7}$ weeks[18]. In the Netherlands there are approximately 30.000 terminations of pregnancy between 5 and 24 weeks annually[19]. Termination for social indications up to 22 weeks is performed in clinics with a special license issued by the Dutch government. These clinics have to adhere to strict regulations and legislation[18]. Terminations for fetal indications (genetic reasons or congenital anomalies) are performed in obstetric units of secondary or tertiary care centers[18].

Due to the rarity of its occurrence, until recently, there was no professional guideline concerning termination of pregnancy for maternal indications without intent for active fetal/neonatal management at the limits of fetal viability. Terminations for maternal indications were briefly mentioned in a footnote of the Dutch guideline concerning late terminations of pregnancy for fetal indications. Terminations for fetal indications are reported to and audited by a committee of health care professionals appointed by the ministries of Health and Justice[20], however, terminations for maternal indications were generally not reported. In February 2016 a revised guideline was published and included recommendations on decision making and management concerning maternal indications. Such terminations are now reported to and audited by an expert panel of medical professionals under the supervision of the Dutch Society of Obstetrics and Gynecology. This committee reviews the cases according to the recommendations described in the recently published national guideline[21]. This is in line with the results of the survey amongst obstetricians and neonatologists (as described in chapter 5) that these cases, due to the complex and highly individualized decision-making process are best audited by a team of expert colleagues as appointed by the Dutch Society of Obstetrics and Gynecology.

Part II: Indicated delivery for hypertensive disorders at the limits of fetal viability with the explicit intention to intervene for fetal indications and active neonatal management

Pregnancy outcome in Dutch women with preeclampsia prior to 26 weeks' gestation

In this group of women maternal complications occurred frequently (50%) and neonatal survival was limited (19%). In the surviving neonates and neonatal morbidity was high (85%) (chapter 6). Neonatal morbidity consisted of necrotizing enterocolitis, intraventricular hemorrhage, sepsis and respiratory distress syndrome or bronchopulmonary dysplasia. These percentages are comparable to other literature describing the outcome of such pregnancies[22-25]. Neonatal survival was poor when preeclampsia occurred prior to 24 weeks' gestation (15%). Surviving neonates were on average 7 days older and their estimated weight was 144 grams higher than non-surviving neonates.

Mode of delivery in preeclampsia prior to 28 weeks' gestation

Following the decision that the mother should deliver in order to secure her health and the fetus is considered viable, another dilemma arises. What is the best mode of delivery with respect to maternal and neonatal outcome? Due to the high frequency of non-reassuring fetal heart rate tracings, fetal malpresentation and often unfavorable cervix some experts recommend scheduled cesarean section in severe early onset preeclampsia[26], whereas others recommend an attempt of vaginal delivery after cervical ripening[27]. As there are no RCT's on this subject several small studies report on mode of delivery in women with preeclampsia prior to 28 weeks' gestation and maternal and neonatal outcome, such as endometritis, postpartum hemorrhage, neonatal birth injury, neonatal death or composite neonatal morbidity, as presented in a systematic review (chapter 7). Planned cesarean section rates varied from 47% to 73.2%[28-32]. Success rates of vaginal delivery varied from 1.8% to 80% and rates for intercurrent cesarean delivery at some time during the process of induction of labor varied from 13% to 51%[28-32]. There were no statistical differences in neonatal and maternal outcome according to mode of delivery, but the data are limited. One study, not included in the review in chapter 7, due to the fact that it did not specifically study women with a gestational age prior to 28 weeks' gestation, addressed mode of delivery in women with preeclampsia and a fetus with very low estimated fetal weight[33]. The study shows a substantial risk of maternal complications in early preterm birth, such as hemorrhage, infection and ICU admission. The risk of the aforementioned serious maternal complications is 23% with a classical cesarean section, i.e. with a vertical incision in the uterus, versus 3.5% when the mother has a vaginal delivery[33]. Furthermore, performing a cesarean section at an extreme premature gestational age has potential consequences in future pregnancies, such as risk of uterine rupture and abnormal placentation[34].

	Mean GA IP* (wk)	Mean GA SP# (wk)	Recurrence rate PE†
van Rijn (2006)	$29^{3/7} \pm 2,5$	38 ± 3.5	28%
Langeveld et al (2011)	30	37 ± 4	35%
Chames et al (2003)	$25^{2/7} \pm 3$	-	55%
van Oostwaard et al (2017)	$25^{0/7} \pm 1$	$35^{4/7} \pm 5$	31%
van Eerden et al (2017)	$24^{5/7} \pm 2$	$35^{6/7} \pm 4$	29%

Table 1. Recurrence rate of preeclampsia in the different studies.
GA = gestational age, IP= index pregnancy, SP= subsequent pregnancy, PE= preeclampsia

In the systematic review (chapter 7) studies concerning neonatal outcome showed no statistical differences in neonatal death or composite neonatal morbidity according to mode of delivery, but again numbers are limited[28,30,31]. However, two older studies report a possible neonatal benefit of a vaginal delivery at gestational ages of 24 to 28 weeks and in very low birth weight infants. Both studies show a lower incidence of respiratory distress syndrome in neonates who were delivered vaginally[35-36].

Subsequent pregnancy outcome and recurrence risk after termination of pregnancy or early delivery for hypertensive disorders

Pregnancy outcome

Pregnancy outcome in women following termination of pregnancy for hypertensive disorders was uneventful in 53% and showed comparable results to an earlier Dutch study[37] strengthening the findings in this thesis. The mean gestational age at delivery was $35^{6/7} \pm 4$ weeks with a mean birth weight of 2571 ± 938 grams compared to $24^{5/7} \pm 2$ weeks with a mean birth weight of 469 ± 124 grams in the index pregnancy. The perinatal mortality in the subsequent pregnancy was 4%. Women with chronic hypertension (CH) delivered on average 3 weeks earlier compared to women who were normotensive.

Recurrence rate

The recurrence rate for preeclampsia was 29% in the study presented in chapter 4 and 31% in the study described in chapter 6. Recurrent early onset preeclampsia, resulting in a delivery prior to 32 weeks' gestation, occurred in 15%-37% of cases in this thesis, compared to 5%-44% in the existing literature to date[37-38] (see table 1). Comparable to what is known from the literature women with chronic hypertension had the highest recurrence rate[38]. One study, by Chames et al, explicitly looked at recurrence of preeclampsia following HELLP syndrome in a previous pregnancy prior to 28 weeks' gestation[39]. The reported recurrence rate of 55% is higher compared to the findings in this thesis (29-31%). Explaining this difference in recurrence rate is difficult, since the study by Chames does not report other risk factors for preeclampsia besides chronic hypertension.

However, differences in research population, such as ethnicity and underlying diseases might be one of the explanations.

Potentially, the recurrence risk in the population with a history of severe early onset preeclampsia described in this thesis was positively influenced by the prescription of low dose aspirin. Indeed, even though this was not statistically significant probably due to small sample size, women who did not receive low dose aspirin had a higher recurrence rate of preeclampsia 23% vs 75%. There is now sufficient literature to support the prescription of low dose aspirin, starting prior to 16 weeks' gestation, in order to reduce the recurrence risk of preeclampsia[40-42]. The World Health Organization as well as the American College of Obstetricians and Gynecologists and the National Institute for Health and Care Excellence (NICE) all recommend low dose aspirin for the prevention of preeclampsia in these high risk women[43-45].

Patient perspective

For the professional reading the research in this thesis, the perspective of the patient provides highly valuable information which should be taken into account when counseling similar patients on the management options in case of severe maternal illness at the limits of fetal viability.

Three former patients share their stories in this thesis. The first is written by a patient who developed preeclampsia prior to 24 weeks' gestation. Her pregnancy was terminated without active neonatal support. The second is written by a patient who developed preeclampsia remote from term in two consecutive pregnancies. Both children were delivered premature and both are now healthy. The third is written by a patient who was born prematurely herself. She describes the challenges she faces every day.

Patient 1

January 2018

I am currently 38 years old. I want to share the story of my first pregnancy in 2007.

October 2007 (gestational age 21 weeks)

I woke up in the middle of the night due to severe stomach pain. I am not sure what the cause might be, but I am immediately worried. I have felt this pain for the last couple of days, but now it is more severe. I am unable to sit or lye down. I am having doubts whether or not to wake my husband because it is in the middle of the night, but finally I wake him, because I cannot stand the pain anymore. Together we decide to call our midwife. She makes a house visit and checks my urine. There is something wrong, I am not completely sure what, but we are sent to the hospital for further evaluation immediately.

After that night our lives changed forever. A period of stress, grief, love, disbelief, incomprehension, doubt but especially fear begins. I was so scared. Scared of what was

going to happen, scared of losing control, scared of being alone, scared of falling asleep and scared of dying……

When I arrived at the hospital I trusted the doctors to take good care of me, however during the next days my situation became worse. I was most worried about my husband. He had to go to work during the day and came to the hospital right after he was finished. I counted the minutes to his arrival, I was afraid to be alone. My urine looked strange, as if there was an omelet floating in it. I started to have neurological symptoms as well; I was seizing and started to drool. Eventually reading and talking became difficult. I did not understand what was going on.

It took about a week before the doctors figured out what was wrong. I was only 21 weeks' pregnant, so at first they did not suspect a pregnancy related condition. A psychologist consulted me, maybe it was all in my head. Furthermore the doctors wanted to rule out liver infection, because recently, we made a trip to South America. However, none of the tests confirmed that diagnosis.

1 week later (gestational age 22 weeks)

I start to lose my clarity. My husband, my mother and my sister are now with me round the clock. The seizures become more frequent. I am so tired, but I am scared of falling asleep. Doctors and nurses are walking in and out of my room. One of the doctors decides that something has to happen right now. I am being transferred to a tertiary referral center, I am told they want to perform an advanced ultrasound to check the baby. First medication is started. The doctors tell me it is magnesium sulphate. I feel really warm and I wet myself. I try to call out, but my voice is not functioning….

After a long night the ambulance comes to pick me up. I have never been in one and I am scared. During the trip I start seizing again. When we arrive in the other hospital the ultrasound shows no major problems with the baby. Then two doctors come to visit me and my husband, I finally hear what is wrong with me. I suffer from HELLP syndrome. It means I am really ill, it is a life threatening condition. They recommend to induce labor in order to save my life.

After this conversation I talk to my mother on the phone and then the severity of my situation finally hits me.

I don't recall much of what happens next, I am sick, really sick, sicker than I thought, sicker than I ever imagined. It was not strange that my body acted so weird.

Labor is induced, and at the same time I am sedated for comfort. I fall in and out of consciousness. Every now and then I see a glimpse of my husband and my mother, they look so sad.

All of a sudden a team of doctors appear. I cannot stand the light, but I can see all the white coats. They are deciding whether I need to be transferred to the ICU, but luckily I am stable enough to stay at the maternity unit..

Labor is really heavy for me. After a long period our son is born….but he is too small to survive.

The next day I am brought to another room to recover. Then the misery really starts. My body and my mind are prepared to take care of a baby, but there is no baby to care for. It is then I realize what had happened in the past days. The conversations with the doctors that I was really sick, the choice to induce labor to save my life. The birth of my son, the grief of my husbands and my own. Psychologists are asked to help guide us through this process.

2018 (11 years later)

We became parents of two beautiful girls. One is nine years old and the other is almost three. During these pregnancies I worried a lot. I tried to enjoy being pregnant, but it was difficult. The fear that something was going to happen never disappeared.

HELLP syndrome left some big scars. It is only since a couple of months that I can fully function again. Especially the physical part of the recovery took a long time, besides the mental recovery. Family, friends and co-workers have been really supportive even though they did not have much knowledge about HELLP syndrome and the residual symptoms.

I have had and still have residual problems that are not easy to explain. I am not able to fully function in my job, and due to the fact that HELLP syndrome is not acknowledged by the social services, results in my illness having financial consequences as well. You can never realize this when you become pregnant. Our lives have been turned upside down and will never be the same again.

Even though my son did not survive, I am grateful to the doctors and nurses who took such good care of me and my family.

Patient 2

Right after I stopped taking birth control pills I became pregnant. I was very happy. However, from the first trimester on I was not feeling well. Early on I felt weak, and I was having urinary tract infections and contractions. I was very tired. No matter what I tried I did not feel better. When I was 20 weeks pregnant I was unable to go to work, due to extreme fatigue. I had the feeling something was not right.

The general physician and the midwife could not find out what was wrong with me. They thought all my complaints were part of a normal pregnancy. They made me feel like I was overreacting. That was really frustrating to me, because I had always been a strong person.

Intuition

Even though I was not worried about the baby, I felt something was wrong. I made all the arrangements for the baby early in my pregnancy, as if there was no time to do that later in my pregnancy. My condition worsened. I felt sicker and even more tired. But for a long period none of the professionals believed me, until the midwife checked my blood pressure during one of the regular checks. It was very high. She sent me to the hospital. The laboratory tests were normal and no proteins were found in my urine. Even though I did not look sick, like one of the young doctors remarked, I felt sick. I had severe stomach pains and I was dyspneic. I was sent home with a web link to more information on preeclampsia and I had to come to the hospital every other day to check my blood pressure and my blood.

Preeclampsia and premature birth

Two days later I was having a check at the hospital. A CTG was made and the baby's heartbeat appeared to be abnormal. By that time I was almost 32 weeks pregnant. All of a sudden I felt a snap and my water broke. The doctors started with tocolysis and gave me drugs for the lungs of the baby. My urine sample did show proteins this time and my laboratory results showed abnormalities. I was very calm and I strangely felt relieved that I was right all along.

I remained very calm. Of course I knew that 32 weeks' was too early, but I could not fully understand the consequences by that time. My blood pressure kept rising and I was given magnesium sulphate. After a while I felt sedated. The drugs to stop the contractions did not work and labor progressed during the night. In the morning I was brought to the delivery rooms and my partner rushed to the hospital. During delivery I was still very calm. For a long time I thought this was because of the magnesium sulphate, but now I know I was calm, because I was too sick to be panicking.

My son was born quickly after my partner arrived. He weighed almost 2 kilograms, which is not so bad for 32 weeks' gestation. My son stayed with me for a short time and was then brought to the neonatal care unit.

After the delivery

After the delivery I was numb. My vision was blurry and I could not focus. I was confused, I told the same story over and over again, but I was not aware of it. I went to see my son, but I could not focus and I could not remember what the doctors told me. When I went to sleep I realized what had happened. There I was in the middle of the night, alone, without my son. I felt lonely and empty. I cried the whole night, I had never been so heartbroken. The next day the iv from my arm was removed and I was no longer hooked up to a monitor. During the day I was brought to my son and during the night I went there on my own. I sat next to the incubator for hours.

After five days, right before I was discharged, one of the doctors sat next to me and asked me if I had any questions. It was then that I first heard the diagnosis of preeclampsia and I realized how sick I had been. I don't know whether I was feeling too sick before, or that no one had told me, but for me this was the first time that it was clear to me and my family what was wrong with me. I realized that if the doctors had caught it earlier, it might have caused less pain and frustration.

Home alone

It felt terrible to leave my son in the hospital, attached to all the tubes. I was still feeling extremely tired and I was unable to do things. I couldn't concentrate, couldn't read and I had severe palpitations. Every day I went to the hospital, where I held my son for hours.

For other people everything went on as usual. For me that was very strange. Nobody understood what I had been through and that I was still feeling sick or how it felt to leave your baby.

When my son was released from the hospital I had no energy to see visitors. It was just me and my son. I sat on the couch and held him in my arms. I still had a lot of complaints and questions. I was not able to do much during the day, was that normal? When I had my postpartum visit, the midwife in the hospital told me to take it easy and that it was normal to feel this way. When I searched the internet I found a lot of information on preeclampsia and after a year everything made sense.

The weeks passed and I still struggled. I felt guilty towards my boss and my co-workers. However, they were very understanding and supported me, unlike the doctor in charge of my work reintegration. He was not very understanding and quickly made a reintegration plan. In the mean time I had a check in a hospital that specializes in early preeclampsia. Here they told me that my symptoms were normal and that it could take years to recover. They also gave me a letter for the doctors at work. It was such a relief, I finally felt someone understood what I was going through.

Repetition

Half a year later my symptoms worsened. First I did not understand why, but then it turned out I was pregnant again. I was very happy, but also very worried. My body did not recover from the first pregnancy and now I was pregnant again. One of my friends gave me a machine to measure my blood pressure myself. When I was 35 weeks pregnant my blood pressure began to rise and I had symptoms I immediately recognized from the first time. I suffered from extreme headaches, light sensations, and for a short period of time I had no vision in one of my eyes. I received medication for my blood pressure and labor was induced the next day. After a painful delivery I could hold my second son in my arms.

Years later

Looking back on both pregnancies I feel sad that I was unable to enjoy either of the pregnancies or the period after giving birth. Physically, I never fully recovered. The problems with concentrating are still there and I am easily tired.

I am happy. Eight years ago I started an online platform, called "Kleine kanjers" to help other parents of premature babies. Furthermore I developed different products and books, one of which being a book for premature babies. The stories I have heard over the years are sometimes heartbreaking and I count my blessings every day. My son is a healthy nine year old, who performs well at school and is the tallest of his class.

Patient 3

I was born 21 years ago at a gestational age of 24 weeks and 6 days. My mother was pregnant with twins. Labor started spontaneously. My brother was born first and weighed 740 grams. I came second and weighed 600 grams. In that time frame, a singleton with the same birthweight would probably not have been given the same opportunity. I was lucky to be part of twins. Because my brother had a birthweight of 740 grams, we were both given the benefit of the doubt. Unfortunately my brother passed away after a couple of days due to a severe intracerebral bleeding. The day my brother died, I had my first surgery. Doctors performed open heart surgery and closed the ductus Botalli. I survived surgery and the period thereafter. I stayed in the hospital for months. However, this period was not without complications. I suffered from gastro-intestinal problems, decubitus, infections, thrombosis in my heart and retinal problems. I received 13 blood transfusions and was on a ventilator for months. Finally, 1.5 months after the due date I was able to go home with my parents.

I asked her mother to look back on the pregnancy and delivery. What she misses the most is the fact that me and my brother were separated at birth and therefore there are no pictures with the two of us together. We both needed such intensive care, that it could not be provided in one place.

I have residual problems from my prematurity. My hearing is impaired and this causes problems in crowded spaces. When I am in a one on one conversation with someone, there are no problems. However, when I am in a crowded room, with lots of background noises, it is very difficult to have a conversation with someone.

Furthermore, I have always experienced problems in school. I had to work really hard for my grades. I have trouble overseeing things, especially when a lot of information is given at once. Besides that, processing the information and acting on it and anticipating on things is very hard for me and costs a lot of energy. Therefore I am always tired.

I did finish high school and started a higher education training. However, due to the pressure and stress of this education I developed a burn-out and psychological problems. I was forced to drop out of college.

Family and friends are very understanding of my situation, but it is sometimes frustrating to explain everything to new people. Now, I spend all of my time on my own project: "Klein meisje maakt een reisje". I give talks on prematurity and my experiences in life. My goal is to gain more knowledge on prematurity and the problems that go with it. I have my own facebook page and Youtube channel. Because of this project I am now in contact with other people born prematurely, with whom I can share my story.

CONCLUSIONS

In cases where the health and the life of the mother are in danger due to severe maternal conditions at the limits of fetal viability, several dilemmas occur. First the decision has to be made whether or not the pregnancy needs to end immediately, and should this question be answered affirmatively, a decision pertaining to active fetal and neonatal management has to be made, based on estimation of fetal viability. Two possible management become apparent: delivery with or without fetal surveillance and subsequent active neonatal management.

In women who develop preeclampsia prior to 26 weeks' gestation maternal complications occurred frequently (50%-68%), neonatal survival was limited (19%) and troubled by complications (85%).

Termination of pregnancy for maternal indications at the limits of fetal viability, without fetal surveillance and active neonatal care is fortunately rare, with an incidence of approximately 18 cases per year in the Netherlands and gradually declining due to changing guidelines on the earliest gestational age and the estimated fetal weight for active neonatal management. The majority of cases concerns hypertensive disorders in pregnancy (12 cases per year).

Subsequent pregnancy outcome after termination of pregnancy for a hypertensive disorder is favorable, with 53% of the pregnancies being uncomplicated. The gestational age at delivery is more than 11 weeks later and the neonatal birth weight is more than 2000 grams higher. The recurrence rate for preeclampsia overall is 29%-31%, when low dose aspirin is prescribed this is 23%. Women with chronic hypertension demonstrate the highest recurrence rate.

RECOMMENDATIONS FOR CLINICAL PRACTICE AND FUTURE RESEARCH

Based on the results of this thesis recommendations can be made regarding counseling and management of women whose health or lives are in danger at the limits of fetal viability.

Termination of pregnancy should be offered to women who develop serious illnesses prior to 24 weeks' gestation. Especially women with preeclampsia are at risk for severe maternal morbidity, whereas postponing delivery does not lead to improved fetal outcome.

Significant variation in management between different centers in the Netherlands is undesirable. Dutch women deserve to be counseled in a similar manner concerning their prospects for maternal morbidity, neonatal management and outcome and future pregnancies.

In counseling parents at the limits of fetal viability it is recommended that all involved medical specialists are voicing the same opinion and present their recommendations as a team. In order to ascertain that both the interests of the mother as the fetus are discussed, these are at a minimum the involved obstetricians and neonatologists. The final decision should be based on both individual patient characteristics as well as parents' preferences.

FUTURE PERSPECTIVES

As neonatal intensive care continues to improve and enables survival at earlier gestational ages and lower birth weights it is prudent to continuously monitor the practice and outcomes to be able to define best-practices in the care of these complicated pregnancies. Therefore, all cases of termination of pregnancy for maternal indications at the limits of fetal viability are now reported to and audited by a team of expert colleagues as appointed by the Dutch Society of Obstetrics and Gynecology. This expert-panel reports back yearly to all members of the Dutch Society of Obstetrics and Gynecology and provides recommendations for management in these cases.

More research is needed to investigate neonatal outcome in severe early onset preeclampsia. A prognostic model in which all of the prognostic parameters are taken into account would be helpful.

As research shows differences in opinion regarding management, an integrated protocol between obstetricians and neonatologists on counseling women suffering from early onset preeclampsia, and their partners on the maternal and neonatal management and outcomes should be developed.

EFERENCES:

1. Seri I, Evans J. Limits of viability: definition of the gray zone. Journal of Perinatology 2008:28, S4–S8
2. Nederlandse richtlijn perinataal beleid bij extreme vroeggeboorte. Available at www.nvog.nl/kwaliteitsdocumenten/richtlijnen
3. Geurtzen R, Draaisma J, Hermens R et al. Perinatal practice in extreme premature delivery: variation in Dutch physicians' preferences despite guideline. Eur J Pediatr. 2016;175(8):1039-46
4. Tromp M, Eskes M, Reitsma JB et al. Regional perinatal mortality differences in the Netherlands; care is the question. BMC Public Health 2009;9:102
5. de Graaf J, Schutte J, Poeran J, et al. Regional differences in Dutch maternal mortality. BJOG 2012;119:582–588
6. Ashimi Balogun OA, Sibai BM. Counseling, management, and outcome in women with severe preeclampsia at 23 to 28 weeks' gestation. Clinical Obstetrics and Gynecology 2017;60:183–189
7. Ganzevoort W, Sibai BM. Temporising versus interventionist management (preterm and at term). Best Practice & Research Clinical Obstetrics and Gynecology 2011;25:463–476
8. WHO recommendations for Prevention and treatment of pre-eclampsia and eclampsia. World Health Organization 2011. Available at www.who.int
9. Anderson JG, Baer RJ, Partridge JC, et al. Survival and Major Morbidity of Extremely Preterm Infants: A Population-Based Study. Pediatrics 2016;138:e320154434
10. Ishii N, Kono Y, Yonemoto N, et al. Outcomes of infants born at 22 and 23 weeks' gestation. Pediatrics 2013;132:62
11. Ancel PY, Goffinet F. Survival and morbidity of preterm children born at 22 through 34 weeks' gestation in France in 2011: Results of the EPIPAGE-2 Cohort Study. JAMA Pediatrics 2015;169:230
12. Stefanelli S, Groom KM. The accuracy of ultrasound-estimated fetal weight in extremely preterm infants: a comparison of small for gestational age and appropriate for gestational age. Aus N Z J Obstet Gynaecol. 2014;54(2):126-131
13. Getahun D, Ananth CV, Kinzler WL. Risk factors for antepartum and intrapartum stillbirth: a population-based study. Am J Obstet Gynecol. 2007;196(6):499–507
14. Tsai LY, Chen YL, Tsou KI et al. The Impact of Small for Gestational Age on Neonatal Outcome among Very Low Birth Weight Infants, Pediatr Neonatol 2015;56(2):101-7
15. Geurtzen R, van Heijst A, Draaisma J et al. Professionals' preferences in prenatal counseling at the limits of viability: a nationwide qualitative Dutch study. Eur J Pediatr. 2017;176(8):1107-1119
16. Taittonen L, Korhonen P, Palomaki O et al. Opinions on the counselling, care and outcome of extremely premature birth among healthcare professionals in Finland. Acta Paediatr 2014;103:262–267
17. www.womenonwaves.org
18. Wet afbreking zwangerschap. Available at www.wetboek-online.nl
19. Jaarrapportage 2015 van de Wet afbreking zwangerschap. Inspectie voor de gezondheidszorg. Utrecht 2017. Available at www.fiom.nl
20. NVOG modelprotocol LZA: Medisch handelen late zwangerschapsafbreking 2007. Available at www.nvog.nl/kwaliteitsdocumenten/richtlijnen
21. Protocol Zwangerschapsbeëindiging op maternale indicatie. Available at www.nvog.nl/kwaliteitsdocumenten/protocollen

22. Gaugler-Senden IP, Huijssoon AG, Visser W et al. Maternal and perinatal outcome of preeclampsia with an onset before 24 weeks' gestation. Audit in a tertiary referral center. Eur J Obstet Gynecol Reprod Biol 2006;128:216-21.
23. Belghiti J, Kayem G, Tsatsaris V et al. Benefits and risks of expectant management of severe pre-eclampsia at less than 26 weeks gestation: the impact of gestational age and severe fetal growth restriction. Am J Obstet Gynecol 2011;205(5):465.e1-6.
24. Bombrys AE, Barton JR, Nowacki EA et al. Expectant management of severe preeclampsia at less than 27 weeks' gestation: maternal and perinatal outcomes according to gestational age by weeks at onset of expectant management. Am J Obstet Gynecol 2008;199:247.e1–247.e6.
25. Budden A, Wilkinson L, Buksh MJ et al. Pregnancy outcome in women presenting with pre-eclampsia at less than 25 weeks gestation. Aust N Z J Obstet Gynaecol 2006;46 407–412.
26. Sibai BM, Barton JR. Expectant management of severe preeclampsia remote from term: patient selection, treatment, and delivery indications. Am J Obstet Gynecol.2007;196:514.e1-514.e9.
27. Alexander JM, Bloom SL, McIntire DD et al. Severe preeclampsia and the very low birth weight infant: is induction of labor harmful? Obstet Gynecol. 1999;93(4):485-8
28. Alanis MC, Robinson CJ, Hulsey TC et al. Early-onset severe preeclampsia: induction of labor vs elective cesarean delivery and neonatal outcomes. Am J Obstet Gynecol 2008;199:262.e1-262.e6
29. Mashiloane CD, Moodley J. Induction or caesarean section for preterm pre-eclampsia. J Obstet Gynecol 2002;22:4.353-356
30. Blackwell SC, Redman ME, Tomlinson M et al. Labor induction for the preterm severe pre-eclamptic patient: is it worth the effort? J Matern Fetal Neonatal Med 2001;10;305-311
31. Nassar AH, Adra AM, Chakhtoura N et al. Severe preeclampsia remote from term: Labor induction or elective cesarean delivery? Am J Obstet Gynecol 2001;179:5.1210-1213
32. Kim LH, Cheng YW, Delaney S. Is preeclampsia associated with an increased risk of cesarean delivery if labor is induced? J Matern Fetal Neonatal Med 2010;23(5): 383-388
33. Reddy UM, Rice MM, Grobman WA et al. Serious maternal complications after early preterm delivery (24–33 weeks' gestation). Am J Obstet Gynecol 2015;213:538.e1–9
34. Lannon SM, Guthrie KA, Reed SD et al. Mode of delivery at periviable gestational ages: impact on subsequent reproductive outcomes. J Perinat Med. 2013;41(6):691-7
35. Regenstein AC, Laros RK Jr, Wakeley A et al. Mode of delivery in pregnancies complicated by preeclampsia with very low birth weight infants. J Perinatol. 1995;15(1):2-6
36. Kitchen W, Ford GW, Doyle LW et al. Cesarean section or vaginal delivery at 24 to 28 weeks' gestation: comparison of survival and neonatal and two-year morbidity. Obstet Gynecol. 1985;66(2):149-57
37. van Rijn BB, Hoeks LB, Bots ML et al. Outcomes of subsequent pregnancy after first pregnancy with early-onset preeclampsia. Am J Obstet Gynecol 2006;195,723–8
38. Langenveld J, Buttinger A, van der Post J et al. Recurrence risk and prediction of a delivery under 34 weeks of gestation after a history of a severe hypertensive disorder. BJOG 2011;118:589–595
39. Chames MC, Haddad B, Barton JR et al. Subsequent pregnancy outcome in women with a history of HELLP syndrome at ≤ 28 weeks of gestation. Am J Obstet Gynecol 2003;188(6):1504-7
40. Henderson JT, Whitlock EP, O'Connor E et al. Low-Dose Aspirin for the Prevention of Morbidity and Mortality From Preeclampsia: A Systematic Evidence Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 112.AHRQ Publication No. 14-05207-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2014.
41. Coomarasamy A, Honest H, Papaioannou S et al. Aspirin for prevention of preeclampsia in women with historical risk factors: a systematic review. Obstet Gynecol. 2003;101(6):1319-32

42. Roberge S, Villa P, Nicolaides K et al. Early administration of low-dose aspirin for the prevention of preterm and term preeclampsia: a systematic review and meta-analysis. Fetal Diagn Ther. 2012;31(3):141-6
43. WHO recommendations for Prevention and treatment of pre-eclampsia and eclampsia. World Health Organization 2011.
44. American College of Obstetricians and Gynecologists. Hypertension in Pregnancy-Practice Guideline 2013.
45. NICE Quality Standard Hypertension in Pregnancy. 2013

Chapter 10

Summary

During pregnancy the health of the mother can be severely compromised by several conditions. On the one hand there are conditions limited to pregnancy, such as pre-eclampsia, and on the other hand pre-existing conditions can emerge or worsen during pregnancy. When this occurs at an extremely early gestational age it can be unclear if the fetus is viable, this is called the grey zone of viability. In these cases two management strategies are available. The first strategy is termination of pregnancy without intention to intervene for fetal indications and without active neonatal management. The other management strategy is termination of pregnancy with intention to intervene for fetal indications and active neonatal management. In these cases maternal- , fetal-, legal- and ethical aspects play an important role.

The aim of this thesis is to provide contemporary information to the professional on termination of pregnancy for maternal indications at the limits of fetal viability, to enable accurate counseling and reduce unwanted practice variation. To reach this aim we investigated:

1. The incidence and different indications for termination of pregnancy for maternal indications, at the limits of fetal viability in The Netherlands
2. The incidence of termination of pregnancy for hypertensive disorders in the Netherlands
3. The outcomes of subsequent pregnancies, specifically pertaining to the recurrence risk of preeclampsia
4. The opinion of Dutch obstetricians and neonatologists regarding management, auditing and reporting cases of termination of pregnancy at the limits of fetal viability.
5. The possible differences in maternal and neonatal outcome following immediate delivery versus expectant management in cases of extreme early onset preeclampsia.
6. The optimal mode of delivery prior to 28 weeks in case of severe early onset preeclampsia.

Part I: Termination of pregnancy at the limits of fetal viability without intention to intervene for fetal indications and without active neonatal management

Maternal and fetal aspects

Literature on termination of pregnancy for maternal indications at the limits of fetal viability is scarce. In **chapter 2** we describe the results of a multicenter, retrospective cohort study on the prevalence and indications of termination of pregnancy for maternal indications in The Netherlands. A total of 177 pregnancies were terminated in a ten year time period, of which 113 terminations were performed after a gestational age of 24 weeks. The majority of the pregnancies were terminated for hypertensive orders in pregnancy (74%), followed by sepsis in the presence of premature rupture of membranes (16%). The mean gestational age at termination was 171 days (GA $24^{3/7}$ weeks) ± 10 days. In the hypertension group the mean gestational age was 173 days (GA $24^{5/7}$) ±

9.7 days as compared to 167 days (GA $23^{6/7}$) ± 10.1 days in the infection group and 162 days (GA $23^{1/7}$) ± 7.0 days for the other indications. The gestational age at termination was significantly higher in the hypertension group compared to the infection group (p=0.006) and the other indications (p<0.001).The perinatal mortality was nearly 100%. Furthermore we found variation in the number of terminations per center. This might, amongst others, have been due to different local interpretation on active neonatal management at the limits of viability in a period where thresholds for active management were subject to gradual change.

As said before 74% of all terminations were performed for hypertensive disorders in pregnancy. In **chapter 3** we looked in more detail to these pregnancies and furthermore we expanded the inclusion period to 15 years in total. A total of 161 women were included (11-12 per year). The mean gestational age at termination was 172 days ($24^{4/7}$ weeks) ± 9.4 days. The main reason to terminate the pregnancy in these cases was rapid maternal deterioration. In 75% management was initially expectant, with a mean interval between admission and start of termination of 9.3 days ± 5.4 days. Maternal morbidity was high with 75% of women developing HELLP syndrome, eclampsia or needed admission to an ICU. The perinatal mortality was 100%. In this study we also aimed to investigate the accuracy of fetal weight estimation on which fetal prognosis was based. For the decision to refrain from fetal monitoring and active neonatal support the following parameters were taken into consideration: gestational age, estimated fetal weight, growth restriction, and lack of interval growth. In 31% of the cases estimated fetal weight was more than 10% underestimated or overestimated compared to the actual birth weight.

In order to counsel these women on future pregnancies and recurrence risk we investigated the pregnancy outcome of the first subsequent pregnancy after termination of pregnancy. These results are described in **chapter 4**. The cohort consisted of 131 women with a termination of pregnancy for hypertensive disorders. Data on subsequent pregnancies was available for 103 women. Eighteen women did not conceive again and seven women had a first trimester miscarriage. There were 72 ongoing pregnancies. The course of these pregnancies was uneventful in 53%. The recurrence rate for preeclampsia was 29%. The mean gestational age at delivery was $35^{6/7}$ ± 4 weeks, which is more than 11 weeks later than in the index pregnancy. The neonatal survival was 96% and the mean birth weight was 2571 ± 938 grams. Women with chronic hypertension had the highest recurrence rate. Furthermore prescription of low dose aspirin is advised, since women who were not given aspirin had a higher recurrence rate.

Chapter 5 describes the results of an online survey amongst obstetricians and neonatologists on management, auditing and reporting cases of termination of pregnancy for maternal indications at the limits of fetal viability. All registered obstetricians (n=197) and neonatologists (n=282) in The Netherlands were invited to participate. The survey

presented 2 hypothetical cases of severe early-onset pre-eclampsia at a periviable gestational age based on historical patient records. The first case was managed by immediate termination, the second case was managed expectantly and directed towards newborn survival. The professionals were asked for their opinions on management, reporting and auditing of the two cases. The overall response rate was 37%. We found that the majority of professionals would be willing to report late termination (after 24 weeks' gestation) for severe maternal disease to medical experts for internal audits, but not for legal auditing. Furthermore we found a significant difference in opinion between the obstetricians and the neonatologists. The first concern of the obstetricians is usually the health of the women, where the first concern of the neonatologists is to achieve a gestational age as favorable as possible for the newborn. These differences in viewpoints should be taken into account when discussing cases in a clinical setting.

Part II: termination of pregnancy for maternal indications at the limits of fetal viability with intention to intervene for fetal viability and active neonatal support

In **chapter 6** we describe the maternal and fetal outcomes and prolongation of pregnancies with severe early onset pre-eclampsia before 26 weeks of gestation. In this group of women maternal complications occurred frequently (50%) and neonatal survival was limited (19%). In the surviving neonates and neonatal morbidity was high (85%). Neonatal morbidity consisted of necrotizing enterocolitis, intraventricular hemorrhage, sepsis and respiratory distress syndrome or bronchopulmonary dysplasia. Neonatal survival was poor when preeclampsia occurred prior to 24 weeks' gestation (15%). Surviving neonates were on average 7 days older and their estimated weight was 144 grams higher than non-surviving neonates. We conclude that women with preeclampsia with an onset prior to 26 weeks' gestation need to be counselled carefully, weighing the risk for maternal complications versus high perinatal mortality.

Chapter 7 describes the results of a systematic review on the maternal and neonatal outcome in vaginal delivery versus caesarean section in severe early onset preeclampsia prior to 28 weeks' gestation. The first aim of this systematic review was to investigate the success rate of attempted vaginal delivery in severe early onset preeclampsia prior to 28 weeks' gestation. Furthermore we aimed to determine if there are any differences in neonatal or maternal outcome according to delivery. Results of 8 studies were included for this review, consisting of retrospective and cohort studies. Planned cesarean section rates varied from 47% to 73.2%. Success rates of vaginal delivery varied from 1.8% to 80% and rates for intercurrent cesarean delivery at some time during the process of induction of labor varied from 13% to 51%. There were no statistical differences in neonatal and maternal outcome according to mode of delivery, but the data are limited. We conclude that, giving the available evidence in the reported studies a trial of labor is a consider-

able option in counseling women with a pregnancy complicated by preeclampsia prior to 28 weeks' gestation due to the similar maternal and neonatal outcome. These women should be counselled that attempted vaginal delivery has a wide range of success and is not easily predicted.

Chapter 8 consists of a new Dutch guideline, which incorporates the clinical aspects and the legal aspects of termination of pregnancy for maternal indications at the limits of fetal viability.

Chapter 9 is the general discussion. The results and findings of the previous chapters are discussed and suggestions are made for management and future research.

Appendices

NEDERLANDSE SAMENVATTING

Tijdens de zwangerschap kan de gezondheid van de moeder ernstig bedreigd worden door verschillende aandoeningen. Deze aandoeningen kunnen veroorzaakt worden door de zwangerschap zelf, zoals bijvoorbeeld preeclampsie, en in andere gevallen kunnen reeds bestaande aandoeningen zich openbaren of verslechteren in de zwangerschap. Wanneer deze bedreiging optreedt in een zeer vroege fase van de zwangerschap, kan het onduidelijk zijn of de foetus overlevingskansen heeft. Dit heet de grijze zone van levensvatbaarheid. In dit soort gevallen zijn er twee mogelijke behandelopties voor de moeder. De eerste optie is het beëindigen van de zwangerschap, zonder te interveniëren op foetale indicatie en zonder actieve neonatale opvang aan te bieden. De andere optie is het beëindigen van de zwangerschap met interventies gericht op foetale overleving en actieve opvang van de neonaat. In deze casuïstiek spelen maternale-, foetale -, juridische - en ethische aspecten een belangrijke rol.

Het doel van dit proefschrift is om de professional te voorzien van uptodate informatie over alle aspecten van zwangerschap beëindiging op maternale indicatie op de grens van foetale levensvatbaarheid, om goed te kunnen counselen en om praktijkvariatie te voorkomen. Om deze doelen te bereiken zijn de volgende zaken onderzocht:

1. De incidentie en de verschillende indicaties voor zwangerschap beëindiging op maternale indicatie op de grens van foetale levensvatbaarheid in Nederland
2. De incidentie van zwangerschap beëindiging voor hypertensieve aandoeningen op de grens van foetale levensvatbaarheid in Nederland
3. De uitkomsten van vervolg zwangerschappen, en in het bijzonder het herhaalrisico op preeclampsie
4. De mening van Nederlandse obstetrici en neonatologen over het beleid van -, het doen van audits over - en het melden van casus van zwangerschap beëindiging op maternale indicatie op de grens van foetale levensvatbaarheid
5. De mogelijke verschillen in maternale en neonatale uitkomsten na een directe beëindiging van de zwangerschap versus expectatief beleid bij ernstige, vroege preeclampsie
6. De optimale partus modus bij preeclampsie voor 28 weken amenorroeduur

Deel I: Zwangerschap beëindiging op de grens van foetale levensvatbaarheid zonder interventies op foetale indicatie en zonder actieve neonatale opvang

Maternale en foetale aspecten

Er is spaarzame literatuur over zwangerschap beëindiging op maternale indicatie op de grens van foetale levensvatbaarheid beschikbaar. In **hoofdstuk 2** worden de resultaten van een multicenter, retrospectieve cohort studie naar de prevalentie van zwangerschap beëindiging op maternale indicatie in Nederland beschreven. Er werden in 10

jaar tijd 177 zwangerschappen beëindigd, waarvan 113 plaats vonden na 24 weken amenorroeduur. Het grootste gedeelte van deze zwangerschappen werd beëindigd vanwege hypertensieve aandoeningen in de zwangerschap (74%), gevolgd door sepsis bij prematuur gebroken vliezen (16%) en overige oorzaken (10%). De gemiddelde amenorroeduur ten tijde van het beëindigen bedroeg 171 dagen (AD $24^{3/7}$) ± dagen. In de hypertensie groep was de gemiddelde amenorroeduur 173 dagen (AD $24^{5/7}$) ± 9.7 dagen vergeleken met 167 dagen ($23^{6/7}$) ± 10.1 dagen in de sepsis groep en 162 dagen ($23^{1/7}$) ± 7 dagen in de overige groep. De amenorroeduur ten tijde van het beëindigen van de zwangerschap was significant hoger in de hypertensiegroep vergeleken met de infectiegroep (p=0.006) en de overige groep (p<0.001). De perinatale sterfte was nagenoeg 100%. Verder vonden we variatie in het aantal zwangerschap beëindigingen tussen de 10 perinatologische centra in Nederland. Dit zou, onder anderen, veroorzaakt kunnen zijn door lokale verschillen in actieve neonatale opvang, in een periode waarin de bestaande richtlijnen over neonatale opvang werden gereviseerd.

Zoals eerder beschreven werd 74% van de beëindigingen verricht vanwege hypertensieve aandoeningen in de zwangerschap. In **hoofdstuk 3** hebben we deze zwangerschappen verder geanalyseerd en tevens is de inclusieperiode met 5 jaar verruimd. In totaal werden er 161 vrouwen geïncludeerd (11-12 per jaar). De gemiddelde amenorroeduur ten tijde van het beëindigen was 172 dagen (AD $24^{4/7}$) ± 9.4 dagen. De meest voorkomende reden om de zwangerschap te beëindigen was snelle verslechtering van de maternale conditie. In 75% van de casus werd er aanvankelijk een afwachtend beleid gevoerd, met een gemiddeld interval tussen de opname en de zwangerschap beëindiging van 9.3 dagen ± 5.4 dagen. De maternale morbiditeit was hoog, waarbij 75% van de vrouwen HELLP syndroom of eclampsie ontwikkelden of werden opgenomen op de intensive care unit. De perinatale sterfte bedroeg 100%.

In deze studie hebben we ook de accuratesse van foetale gewichtsschatting door echoscopisch onderzoek onderzocht, op basis waarvan de foetale prognose werd gebaseerd. Om te komen tot de beslissing om eventueel niet te interveniëren op foetale indicatie werden de volgende parameters bekeken: amenorroeduur, geschat foetaal gewicht, groei-restrictie en de afwezigheid van groei tussen 2 metingen. In 31% van de gevallen week het geschatte gewicht meer dan 10% (zowel overschatting als onderschatting) van het daadwerkelijke geboortegewicht.

Om deze vrouwen goed te kunnen counselen over volgende zwangerschappen en de herhalingskans, verrichtten we een studie naar de zwangerschapsuitkomst in een volgende zwangerschap van deze groep vrouwen. De resultaten worden beschreven in **hoofdstuk 4**. Het cohort bestond uit 131 vrouwen die een zwangerschap beëindiging ondergingen vanwege hypertensieve aandoeningen in de zwangerschap. Van 103 vrouwen waren de uitkomsten van vervolgzwangerschappen beschikbaar. Achttien werden niet meer zwanger en bij 7 vrouwen was er sprake van een vroege miskraam. Er waren

72 doorgaande zwangerschappen, bij 53% verliep de zwangerschap ongecompliceerd. De herhalingskans op preeclampsie was 29%. De gemiddelde amenorroeduur tijdens de bevalling was $35^{6/7}$ week ± 4 weken, dit is 11 weken langer dan in de index zwangerschap. De neonatale overleving was 96% en het gemiddelde geboortegewicht bedroeg 2571 gram ± 938 gram. Vrouwen met chronische hypertensie hadden het hoogste herhalingsrisico. Verder wordt het profylactisch voorschrijven van laag gedoseerde aspirine geadviseerd, aangezien het feit dat de vrouwen die dit niet kregen voorgeschreven een veel hogere herhalingskans hadden.

Hoofdstuk 5 beschrijft de resultaten van een online survey onder perinatologen en neonatologen naar het beleid, het auditen en het rapporteren van zwangerschap beëindiging op maternale indicatie op grens van foetale levensvatbaarheid. Alle geregistreerde perinatologen (n=197) en neonatologen (n=282) in Nederland werden uitgenodigd. De survey bevatte twee hypothetische casus over ernstig vroege preeclampsie, gebaseerd op echte casuïstiek. In de eerste casus bestond het beleid uit een zwangerschap beëindiging, in de tweede casus werd een expectatief beleid gevoerd om een levensvatbare termijn voor de foetus te bereiken. De professionals werd gevraagd om hun mening ten aanzien van het beleid, auditten en rapporteren van deze casus. De respons rate bedroeg 37%. Het grootste gedeelte van de professionals was bereid deze casus van late zwangerschap beëindiging (> AD 24 weken) op maternale indicatie te melden aan medische experts voor interne audits, maar niet voor juridische toetsing. Verder vonden we een opvallende discrepantie tussen de meningen van de perinatologen en neonatologen. De primaire zorg voor de perinatoloog is de gezondheid van de moeder, terwijl de primaire zorg van de neonatologen ligt bij de grootste kans op overleving voor de neonaat. Met dit verschil in uitgangspunt zou rekening gehouden moeten worden als dit soort casus in de praktijk wordt besproken met de verschillende professionals.

Deel II: Zwangerschap beëindiging op maternale indicatie op de grens van foetale levensvatbaarheid met intentie tot interveniëren op foetale indicatie en actieve neonatale opvang

In **hoofdstuk 6** beschrijven we de maternale en foetale uitkomsten en verlenging van zwangerschappen, gecompliceerd door ernstige vroege preeclampsie voor een amenorroeduur van 26 weken. In deze groep vrouwen kwamen maternale complicaties frequent voor (50%) en neonatale overleving was beperkt (19%). Van de overlevende neonaten had een hoog percentage complicaties (85%). De neonatale complicaties bestonden uit necrotiserende enterocolitis, intraventriculaire bloedingen, sepsis en respiratoir distress syndroom of bronchopulmonale dysplasie. De neonatale overleving was slecht indien preeclampsie optrad voor 24 weken amenorroeduur (15%). Overlevende neonaten waren gemiddeld 7 dagen ouder bij de geboorte en hadden een geschat geboortegewicht

wat 144 gram hoger was dan bij de niet overlevende neonaten. Tijdens de counseling van deze vrouwen, moet een afweging gemaakt worden tussen de kans op maternale complicaties en de hoge kans op neonatale sterfte.

Hoofdstuk 7 beschrijft de resultaten van een systematische review naar maternale en neonatale uitkomsten tijdens vaginale bevalling vergeleken met sectio caesarea bij vrouwen met ernstige, vroege preeclampsie voor een amenorroeduur van 28 weken. Het eerste doel van deze review was het bepalen van de succeskans van een vaginale baring bij vrouwen met ernstige vroege preeclampsie (voor AD 28 weken). Verder wilden we onderzoeken of er verschillen in maternale en neonatale uitkomsten bestaan afhankelijk van de modus partus. De resultaten van 8 studies konden worden gebruikt voor analyse, dit betroffen retrospectieve studies en een cohort studie. De kans op een geplande sectio varieerde van 47% tot 73.2% tussen de verschillende studies. De succeskans op een vaginale baring varieerde van 1.8% tot 80% en de kans op een secundaire sectio na inductie van de baring bedroeg 13% tot 51%. Er waren geen significante verschillen in neonatale en maternale uitkomsten tussen de verschillende wijzen van bevallen, maar de getallen in de groepen zijn klein. We concluderen dat, gegeven de beschikbare bewijslast in de geselecteerde studies, een poging tot vaginale baring een redelijke optie is in geval van ernstige vroege preeclampsie voor 28 weken. Er zijn immers geen verschillen in uitkomsten aangetoond. Deze vrouwen zouden verder gecounseld moeten worden over het feit dat de succeskans van een vaginale baring variabel is en moeilijk te voorspellen.

Hoofdstuk 8 bevat een nieuw Nederlands modelprotocol over zwangerschap beeindiging op maternale indicatie op de grens van foetale levensvatbaarheid, welke de klinische en juridische aspecten incorporeert.

Hoofdstuk 9 is de algemene discussie. In dit hoofdstuk worden de meest relevante bevindingen van de andere hoofdstukken bediscussieerd en voorts worden er suggesties gedaan voor beleid en toekomstig onderzoek.

PATIËNTENPERSPECTIEF

Patiënt 1

Oktober 2007: midden in de nacht word ik wakker van de pijn bij mijn middenrif of maag. Ik weet niet zo goed wat het is, maar het voelt niet goed. Ik heb het al een paar dagen, maar niet zo heftig als nu. Moet ik liggen, zitten of lopen? Ik kan niet zitten of lopen, want dan heb ik het gevoel dat ik ga vallen en de pijn wordt eigenlijk alleen maar erger. Hoe laat is het eigenlijk? Kan ik mijn man al wakker maken? Misschien moet ik toch maar gaan slapen en gaat het weer over. Vijf minuten duren eigenlijk toch wel erg lang, de pijn is niet uit te houden. Toch maar mijn man wakker maken. Kan ik de verloskundige al bellen? Het is nog zo vroeg. Hij besluit toch te bellen en ik moet gelijk urine opvangen. Het duurt niet lang voordat de verloskundige er is. Waarom ik niet eerder had gebeld? Geen idee, we wilden ook niet voor niets bellen.

De urinetest geeft aan dat er iets niet goed is. Wat weten we niet, maar we gaan naar het ziekenhuis.

Na deze nacht is ons leven compleet veranderd. Een periode van verdriet, verlies, onbegrip, onzekerheid, liefde, pijn, onwetendheid, maar vooral de angst. Ik ben zo ontzettend bang geweest. Bang voor wat er ging gebeuren, bang om de controle van mijn eigen lichaam te verliezen, bang om alleen te zijn en om in slaap te vallen, bang om dood te gaan…

Toen ik in het ziekenhuis kwam, vertrouwde ik erop dat ik in goede handen was. Het klopt dan niet voor je gevoel dat je zieker en zieker wordt. Het was bijna niet uit te leggen hoe ik me voelde. Ik maakte me het meeste druk om mijn man. Hij moest overdag gewoon werken en kwam naar het ziekenhuis zodra het kon. Ik telde de minuten af; ik durfde niet meer alleen te zijn. Het overgeven werd steeds meer, op mijn urine dreef "een omelet", ik viel achterover omdat ik spastische aanvallen had, ik begon soms te kwijlen waar ik geen controle over had, lezen en praten ging ook steeds moeizamer. Waarom ging het alleen maar slechter? Waarom greep niemand in? Ja, ik was jong en ja, ik was nog maar 21 weken zwanger, maar iedereen zag dat het niet goed met me ging. Naar de wc gaan was al een uitje op zich, ik wist niet hoe snel ik weer naar mijn bed moest komen. Zodra ik begon te lopen, begon alles te draaien. Mijn hele lijf begon weer te trillen zodra ik ging liggen.

Het duurde ruim een week voordat iemand echt ingreep. Er werd niet gekeken naar de zwangerschap, maar naar eventuele andere oorzaken. Zo kwam er bijvoorbeeld een psycholoog met een vragenlijst, omdat ik had aangegeven ooit bij een psycholoog geweest te zijn. Maar er werd ook gedacht aan hepatitis, omdat we in Costa Rica op vakantie waren geweest.

1 week later: mijn helderheid is nog verder weggezakt. Mijn man, mijn moeder en zus zitten steeds op de gang. De spastische aanvallen komen steeds vaker. Ik ben zo ontzet-

tend moe, ik zou zo graag even willen slapen, maar ik durf niet. Wat kan er gebeuren als ik in slaap val? Er komen steeds artsen en verpleegsters binnen. Een van de artsen heeft besloten dat er acuut iets moet gebeuren; morgen word ik naar een academisch ziekenhuis gebracht voor een echo en ik krijg magnesium toegediend. Ik roep nog dat ik in bed lig te plassen, maar het schijnt er allemaal bij te horen. Ik weet niet wat me overkomt. Een enorme piep in mijn oren, het lijkt wel of ik flauw ga vallen. Kan iemand me vertellen of dit wel of niet goed is? Ik wil wel iets zeggen, maar mijn stem komt er niet uit.

Na een hele onrustige nacht worden we eindelijk opgehaald om met de ambulance naar het academische ziekenhuis te gaan. Ik dacht dat het wel een leuk uitje zou zijn, even weg uit het kamertje waar ik al een tijdje lig. We laten alle spullen liggen aangezien we 's middags toch weer zullen komen. Ik heb nog nooit in een ambulance gelegen, dat is al spannend genoeg. Ik maak er niet veel van mee; ik heb al dagen/nachten niet geslapen en ik zou zo graag mijn ogen even dicht willen doen, ik ben zo moe. Opeens hoor ik de sirene van de ambulance gaan. In mijn beleving zijn we uren onderweg. Ik krijg weer van die spastische aanvallen.

Met bed en al rijden we door het ziekenhuis richting de afdeling gynaecologie. De wachtruimte is best vol en ik word in de gang geparkeerd. Al snel worden we opgehaald voor de echo. Gelukkig bleek er niets met het kindje aan de hand wat steeds wel gedacht werd.

Niet veel later lig ik op de verpleegafdeling en hebben we een gesprek met twee artsen. Het is niet goed, ik ben te ziek en het enige wat moet gebeuren is dat het kindje eruit moet, want zo kan het niet langer.

Als ik mijn moeder aan de telefoon heb, komt pas het besef...wat is er in allemaal aan de hand? Waar heb ik iets gemist? Dit was namelijk niet het doel, we zouden alleen een echo maken om na te kijken of er iets was met het kindje.

Ik merk dat ik in die korte tijd nog weinig mee maak van het hele gebeuren. Ik ben echt ziek...zieker dan ik dacht...zieker dan ik me kon voorstellen. Dat mijn lichaam zo raar deed, was dus niet zo gek. De bevalling wordt opgewekt, maar tegelijk word ik ook in slaap gehouden om op krachten te komen. Af en toe vang ik een glimp op van Thijs en mijn moeder...wat een verdriet...en ik zak weer weg. Opeens staat er een heel team aan artsen boven mijn hoofd. Ik kan het licht niet verdragen, maar al die witte jassen zie ik wel. Wordt het IC of blijf ik toch liggen? Ik mag toch op de afdeling blijven liggen.

De bevalling kost veel energie. Na meerdere keren persen komt Ties ter wereld in de vruchtzak...alleen helaas niet levend.

Toen ik de woensdagochtend naar een kamertje werd gebracht, begon de volgende ellende. Mijn lichaam en mijn hoofd waren ingesteld om te zorgen, maar er was niets om voor te zorgen. En toen kwam eindelijk pas het besef wat er de vorige dag allemaal gebeurd was. Het gesprek dat je eigenlijk wel heel erg ziek bent, dat de bevalling werd

ingezet, omdat dat nog de enige manier was om beter te worden. Ties die geboren was, het verdriet van mezelf, maar ook van mijn man. Er werden daarom psychologen ingezet om dit gesprek aan te gaan.

2018

Thijs en ik zijn ouders geworden van 2 prachtige dochters. Sarah is bijna 9 en Emma alweer 2 ½. De zwangerschappen gingen niet vanzelf en waren absoluut niet onbevangen. Ik heb wel geprobeerd ervan te genieten, maar de angst dat het mis zou gaan, was altijd aanwezig.

Het is niet niks wat het Hellp-syndroom heeft aangericht. Sinds een paar maanden heb ik pas het idee dat ik weer wat meer uit het leven kan halen. Niet het psychische proces duurde 10 jaar, maar wel echt het lichamelijke. Mijn familie, vrienden en collega's hebben altijd begrip gehad voor het langdurige herstel, terwijl er eigenlijk zo weinig bekend is over de restverschijnselen. Daar zijn we juist heel erg tegenaan gelopen. Ik heb heel lang blijvende klachten gehad en nog steeds. Het revalidatiecentrum heeft hierin ook een belangrijke rol gehad. Omdat je niet kunt aantonen dat er iets is, zit je in een grijs gebied. Omdat ik door de restverschijnselen minder kan werken en het UWV het Hellp-syndroom niet erkent, hebben we uiteindelijk ook nog met financiële nadelen te maken. Je staat bij dit hele proces niet stil op het moment dat je het ziekenhuis uitloopt. Je hele leven staat op zijn kop en het wordt nooit meer hetzelfde.

Ties heeft het niet gered, maar ik ben de artsen en de verpleegkundigen altijd heel erg dankbaar geweest voor hun deskundigheid en alle goede zorgen die mijn familie en ik hebben gehad.

Patiënt 2

Bijna meteen nadat ik stopte met de pil bleek ik zwanger te zijn van mijn eerste zoon. Dit was een grote verrassing, maar de zwangerschap was erg gewenst. Toch verliep het niet vlekkeloos. Al vroeg in mijn zwangerschap kreeg ik last van terugkerende blaasontstekingen en harde buiken en ik voelde me niet goed. Ik was constant enorm vermoeid, ook na het eerste trimester, en had het gevoel dat er iets niet goed was. Al voordat ik 20 weken zwanger was moest ik stoppen met werken en meldde ik me ziek.

De huisarts en de verloskundige namen mijn klachten niet serieus en zeiden zelfs allebei dat "de ene vrouw nou eenmaal beter met een zwangerschap kan omgaan dan de andere". Met andere woorden: ik overdreef en ik stelde me aan. Dit gaf me een machteloos gevoel en ik voelde me weggezet als een slappeling en een aansteller. Dat vond ik heel erg, want zo kende ik mezelf juist helemaal niet.

Voorgevoel

Hoewel ik niet echt ongerust was over de gezondheid van mijn baby, wist ik zeker dat er iets niet goed was en dat ik deze zwangerschap niet tot het eind zou voldragen. Ik wilde alles ruim van tevoren geregeld hebben, ik stond er op dat we al over een naam besliste en dat we naar het gemeentehuis gingen voor de akte van erkenning. Kleertjes kocht ik daarentegen nauwelijks, want ik was er van overtuigd dat hij die toch nog niet meteen zou dragen. Ik kocht voor het idee een paar shirtjes in maat 56, maar zei tegen mijn moeder dat ik het gevoel had dat we meer voorlopig nog niet nodig zouden hebben.

Intussen voelde ik me steeds zieker en vermoeider worden. Toch was er geen deskundige die daar op inging, totdat ik bij een controle bij de verloskundige een hoge bloeddruk bleek te hebben. Hoewel er geen eiwitten in mijn urine werden aangetroffen, stuurde ze me toch meteen door naar het ziekenhuis. Ook daar werden geen eiwitten in mijn urine aangetroffen en bleken mijn nier- en leverwaarden normaal, mijn bloed was volgens de gynaecoloog "alleen iets ingedikt".

Tijdens een van deze controles zei een jonge arts-assistent dat hij me niet ziek over vond komen, terwijl ik nota bene bijna niet kon zitten en praten door de pijn in mijn leverstreek, zij en rug. Ik werd naar huis gestuurd met een notitieblaadje met een link naar de website met de NVOG met de symptomen van pre-eclampsie. Die moest ik maar even goed doornemen, maar wanneer je dit nooit eerder hebt ervaren, is het erg lastig om te begrijpen wat ze precies bedoelen met bijvoorbeeld een "bandgevoel", waarvan ik achteraf weet dat dat dus was wat ik had. Wel moest ik om de paar dagen terugkomen voor controles.

Pre-eclampsie en een vroeggeboorte

Tijdens de laatste van deze controles moest ik aan de CTG en bleek de hartslag van mijn zoon afwijkend te zijn. Toen ik na anderhalf uur nog steeds aan het CTG lag, hoorden we een hard knappend geluid via de monitor. Tegelijkertijd voelde ik dat mijn broek kletsnat werd. Mijn vliezen waren gebroken. Ik werd naar een andere ruimte gebracht en kreeg een echo en weeënremmers. Mijn urine en bloed werden weer onderzocht en dit keer werden er wel eiwitten aangetroffen en bleken mijn leverwaarden flink afwijkend te zijn. Gek genoeg was het enige wat ik kon denken "zie je wel! Ik wist dat ik me niet aanstelde en dat er iets niet goed was!" Het klinkt raar, maar het voelde als een enorme opluchting dat ik me alles blijkbaar niet verbeeld had en ik echt ziek bleek te zijn.

Ik bleef heel rustig en had sterk het gevoel dat alles goed zou komen en mijn zoon al snel geboren zou worden, precies zoals ik al die tijd al voorvoeld had. Ondanks de weeënremmers die ik kreeg, want ik voelde al direct dat die geen uitwerking hadden en dat de weeën steeds sterker werden. Natuurlijk was 32 weken veel te vroeg, maar op dat moment had ik geen idee wat dat voor gevolgen zou hebben.

Al snel bleek mijn bloeddruk erg te stijgen en kreeg ik een infuus met magnesiumsulfaat. Dit was heel naar, ik voelde me hier even heel ziek door en het was een vreselijk gevoel om de medicijnen letterlijk door mijn lichaam te voelen gaan. Maar daarna werd ik heel suf en ging alles een beetje aan me voorbij.

Ik lag die nacht helemaal alleen op bed en liet alles rustig over me heen komen. Toch zetten de weeën gewoon door en ook toen ze elkaar sneller op begonnen te volgen bleef ik rustig liggen en dacht steeds, er komt zo wel een verpleegkundige bij me kijken, zoals ze gezegd hadden. De nacht ging in een waas aan me voorbij en had ik niet door hoeveel tijd er verstreek. Elke wee ving ik rustig op en ik vond het eigenlijk wel fijn om alleen te liggen.

Heel vroeg in de ochtend kwam de verpleegkundige eindelijk bij me kijken en vroeg me waarom ik niet op de bel had gedrukt. Ik moest mijn vriend bellen dat hij moest komen en werd direct naar de verloskamer gebracht. Nog steeds was ik heel rustig, ook tijdens de bevalling. Ik voelde me alsof ik zware kalmeringsmiddelen had gekregen. Lang heb ik gedacht dat dit door de magnesiumsulfaat kwam, maar sinds de geboorte van mijn tweede zoon (waarbij ik hetzelfde middel kreeg maar niet versuft was, ze waren er toen veel sneller bij) weet ik dat ik waarschijnlijk gewoon erg ziek ben geweest en daardoor zo suf was.

Binnen een uur was mijn zoon geboren. Mischa was erg klein, maar gelukkig had hij met twee kilo een heel mooi gewicht voor deze zwangerschapstermijn. Hij mocht heel even bij me liggen, maar ik kon hem niet goed zien, en al heel snel moest hij naar de couveuseafdeling.

Na de bevalling

De eerste uren na de bevalling zag ik mensen dubbel door elkaar heen bewegen zoals je wel eens in films ziet, kon ik me niet concentreren en vertelde steeds hetzelfde verhaal opnieuw zonder dat ik dat door had. Ook toen ik een paar uur later naar Mischa mocht, kon ik hem niet goed zien en kon ik niets van wat de artsen en verpleegkundigen aan ons vertelden onthouden.

Toen ik 's avonds moest gaan slapen kwam alles als pas echt bij me binnen. Daar lag ik dan, met een lege buik, terwijl mijn baby die nog in mijn buik hoorde te zitten een verdieping hoger helemaal alleen in een couveuse aan allemaal slangetjes lag. Doordat ik nog steeds aan het infuus en aan de monitor lag kon ik niet naar hem toe. Ik voelde me leeg, eenzaam en verscheurd. Ik ben nog nooit zo verdrietig geweest als toen en heb de hele nacht gehuild.

De volgende dag mocht het infuus er uit en werd de monitor losgekoppeld. Overdag werd ik met bed en al naar de couveuseafdeling gereden, maar 's avonds liep ik zelf, op mijn sokken naar hem toe en zat ik bij de couveuse. Het deurtje durfde ik niet open te doen, ik had geen idee of dat wel mocht, maar ik zat op een kruk uren naar hem te kijken.

Vlak voor mijn ontslag, vijf dagen later, kwam er een verloskundige naast me op bed zitten en vroeg of ik nog vragen had. Toen pas kwam ik er achter dat ik pre-eclampsie had gehad en besefte ik hoe ziek ik eigenlijk was geweest. Ik weet niet of het komt doordat ik al die tijd zo suf was geweest, maar naar mijn idee had niemand me dit tot nog toe verteld en ook mijn moeder, die vroeger verloskundige is geweest, wist het niet. Pas nu kwam langzaam het besef dat wanneer mijn ziekte op tijd was (h)erkend, me misschien veel pijn en frustratie bespaard was gebleven.

Alleen naar huis

Ik vond het vreselijk om naar huis te moeten en mijn zoon achter te moeten laten. Nog steeds was ik extreem moe en kon ik helemaal niets. Ik kon me niet concentreren, kon niet lezen en had last van een raar jagend en bonzend hart, klachten die mijn moeder jaren later herkende toen zij last van hartritmestoornissen kreeg. Toch reed ik elke dag twee of drie keer in mijn eentje heen en weer naar het ziekenhuis, waar ik zo veel mogelijk met Mischa buidelde.

Voor de buitenwereld ging het leven gewoon door, alsof er niets gebeurd was. Dat voelde heel vreemd. Niemand begreep wat ik had meegemaakt, dat ik me nog steeds ziek voelde, en hoe het was om je baby elke dag alleen achter te moeten laten in het ziekenhuis.

Na drie lange weken mocht Mischa eindelijk mee naar huis, waar ik heel de dag met hem op mijn borst op de bank lag. Als de telefoon ging nam ik die niet op en ik hield de paar mensen die contact opnamen zo veel mogelijk af. Ik had gewoon geen energie om te praten en was alleen maar gefocust op Mischa, die extreem veel huilde. Het leek me logisch dat hij iets in te halen had na al die tijd dat hij alleen in het ziekenhuis had gelegen.

Nog steeds liep ik met heel veel vragen rond over wat er nu precies gebeurd was en ik kon bijna niets doordat ik nog steeds zoveel klachten had. Nazorg was er echter niet, bij de nacontrole bij de verloskundige in het ziekenhuis werd me alleen gezegd dat ik "maar even lekker rustig aan moest doen". Door eindeloos op internet te zoeken begonnen na ongeveer een half jaar alle puzzelstukjes op hun plek te vallen.

Nog steeds niet de oude

Weken later, toen mijn verlof inmiddels voorbij was, voelde ik me nog steeds uitgeput en tot bijna niets in staat. Mijn baas en collega's waren begripvol toen ik na mijn verlof nog niet kon gaan werken, maar de Arbo-arts waar ik me moest melden niet. Op mijn reactie dat ik alleen de reis naar mijn werk al niet aankon, zei hij dat dat dan jammer was, maar dat hij daar ook niets aan kon veranderen. Hij pakte pen en papier en maakte een schema waarmee ik binnen drie weken weer volledig aan het werk zou zijn.

Inmiddels had ik gelukkig een onderzoek gehad in het academische ziekenhuis en daar gaven ze me een brief die ik naar de Arbo-arts kon sturen. Hier werd me verteld dat mijn klachten heel normaal waren en dat ze nog wel jaren konden aanhouden en misschien nooit meer helemaal zouden verdwijnen. Dat luchtte zo op! Het had allemaal zoveel stress opgeleverd en na maandenlang tobben voelde ik me eindelijk begrepen.

Herhaling

Toen Mischa een half jaar oud was, werden mijn klachten opeens weer erger. Dat kon toch helemaal niet? Ik bleek weer zwanger te zijn, dit keer niet gepland. Hoewel ik blij was, was ik vooral heel ongerust en bang dat ik weer pre-eclampsie zou krijgen. Mijn lichaam was nog niet eens hersteld van de vorige keer. Kon mijn lichaam deze zwangerschap überhaupt wel aan en zou alles zich herhalen?

Van een vriendin kreeg ik een bloeddrukmeter te leen zodat ik zelf mijn bloeddruk kon controleren. In week 35 was mijn bloeddruk weer net zo hoog als toen ik werd opgenomen in mijn eerste zwangerschap. Ik belde het ziekenhuis en moest meteen komen, en bleek inderdaad weer pre-eclampsie te hebben. Dit keer herkende ik bijna alle symptomen. Ik zag sterretjes en lichtvlekken, en had enorme hoofdpijn, een duidelijk herkenbaar bandgevoel om mijn hoofd en zag zelfs even aan één kant niets. Weer kreeg ik een infuus met magnesiumsulfaat en de volgende ochtend werd direct de bevalling ingeleid omdat dit op deze termijn (inmiddels bijna 36 weken) de veiligste optie was.

Dit keer was ik tijdens de bevalling niet versuft, blijkbaar doordat ze er nu zo snel bij waren en ik veel minder ziek was dan de vorige keer. Van deze bevalling herinnerde ik me achteraf elk kleinste detail. Zoals ook de vele keren dat er geprikt moest worden om een infuus te plaatsen, omdat mijn aderen nog zo "kapot" waren van de vorige keer.

Jaren later

Nog steeds kan ik soms verdrietig worden als ik er aan denk dat ik nooit een onbezorgde zwangerschap en kraamtijd heb gehad. Lichamelijk ben ik nooit meer helemaal de oude geworden. De concentratieproblemen zijn uiteindelijk nooit helemaal weggegaan en ik ben nog steeds erg gevoelig voor prikkels, waardoor ik sneller vermoeid ben.

Toch ben ik vooral blij. Acht jaar geleden richtte ik Kleine Kanjers op, een platform en webshop voor ouders van premature, en ik maakte verschillende boeken en producten, waaronder het Babyboek voor Premature. De verhalen die ik de afgelopen jaren heb gelezen en gehoord zijn soms hartverscheurend en ik ben me er enorm van bewust wat een geluk wij hebben gehad en hoeveel erger het had kunnen zijn. Mischa is inmiddels negen, is kerngezond, doet het heel goed op school en is een van de langste van zijn klas.

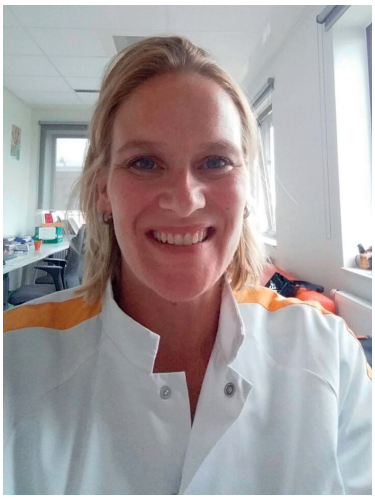
Patiënt 3

Amber werd 21 jaar geleden geboren na een zwangerschap van 24 weken en 6 dagen. Haar moeder was zwanger van een tweeling. De bevalling kwam spontaan op gang. Haar broer werd als eerste geboren en woog 740 gram. Hierna werd Amber geboren, zij woog 600 gram. Er is nooit een oorzaak gevonden van de vroeggeboorte. In die tijd zou zij, als zij een eenling was geweest met hetzelfde geboortegewicht, wellicht niet behandeld zijn. Omdat ze volgens de protocollen niet levensvatbaar zou zijn. Zij heeft het geluk gehad dat ze de helft van een tweeling was, waarbij haar broertje voldoende geboortegewicht had en stabiel leek. Amber kreeg daardoor ook het voordeel van de twijfel. Helaas overleed haar broer enkele dagen na de bevalling aan de gevolgen van een grote hersenbloeding. Amber zelf werd op die dag geopereerd aan haar hart, waarbij de ductus Botalli werd gesloten, zij woog op dat moment slechts 520 gram. Amber overleefde de operatie en de periode erna. Zij verbleef in totaal 4,5 maand in het ziekenhuis. Daar kreeg ze ook nog een onverklaarbare maagaandoening, een doorligplek met ontstekingen, infecties, twee bloedstolsels in één van de bloedvaten in haar hart, 13 bloedtransfusies, netvliesbeschadiging aan haar ogen, is ze ontelbare keren geprikt en heeft ze maandenlang aan de beademing gelegen. Uiteindelijk mocht ze 1,5 maand na de fictieve uitgerekende datum naar huis. Amber heeft aan haar vroeggeboorte wel wat problemen overgehouden. Haar gehoor is beschadigd, waar ze met name in drukke ruimtes veel last heeft. Eén op één gesprekken zijn heel goed te doen, maar in drukke ruimtes met veel omgevingsgeluid, is het moeilijk om een gesprek te volgen. Naast de gehoorschade heeft Amber het op school altijd heel moeilijk gehad. Ze moest hard werken, voor vaak een mager resultaat. Zij heeft moeite met het overzien van dingen, vooral als er veel informatie tegelijk wordt gegeven. Daarnaast kost het verwerken van de informatie en daar vervolgens naar handelen veel energie en concentratie. Hierdoor is zij snel vermoeid. Ook heeft ze veel moeite met verbanden leggen. Ze vindt het lastig om vooruit te denken, bijvoorbeeld bij oorzaak en gevolg. Zij heeft haar middelbare school (kader) afgerond. Hierna is ze begonnen aan een mbo opleiding tot begeleider specifieke doelgroepen. Echter door de druk en de stress van de opleiding ontwikkelde zij een burn-out en een conversie-stoornis en moest daardoor gedwongen stoppen met de opleiding. Op dit moment heeft zij een tussenjaar. Er is veel begrip voor haar situatie bij haar familie en vrienden, maar soms vindt ze het wel eens lastig om haar situatie steeds te moeten uitleggen aan vreemden.

"Wat mijn moeder in die tijd erg gemist heeft is dat er geen ruimte was om ons, mijn tweelingbroer en ik, op dezelfde afdeling te behandelen. Wij zijn direct na onze geboorte gescheiden van elkaar omdat de zorg van twee zulke extreem te vroeggeborenen te intensief was voor de verzorgers op 1 afdeling. Daardoor is er niet één foto waar wij allebei op staan. Dat vind ze heel erg."

Zij benut haar tijd op dit moment met haar eigen project Klein Meisje maakt een Reisje. Ze geeft gastcolleges over haar ervaringen als exprematuur. Het doel is om meer bekendheid te creëren bij mensen over prematuriteit en tegen welke problemen je als gevolg hiervan, in het dagelijks leven, aan kan lopen. Zij heeft een facebook pagina en houdt een YouTube kanaal bij, die beide deze naam draagt. Door haar project heeft ze ook contact met andere ex-prematuren.

OVER DE AUTEUR



Leonoor van Eerden is geboren op 28 maart 1978 in Groningen als jongste van drie dochters. Na de basisschool gaat ze naar het Praedinius Gymnasium in Groningen, waar ze in 1996 eindexamen doet. In de zomer van 1996 start ze met de Geneeskunde Opleiding aan de Vrije Universiteit te Amsterdam. In 2000 behaalt ze haar doctoraal en in 2002 rondt ze cum laude haar post-doctorale fase af.

Van 2002 tot 2006 werkt ze als assistent niet in opleiding, eerst in het Kennemer Gasthuis (opleider: Dr. J.P. Lips) en later op de afdeling gynaecologische oncologie in het VU Medisch Centrum (hoofd: prof. Dr. R.H.M. Verheijen).

In 2006 start ze met de opleiding tot gynaecoloog deels in het Kennemer Gasthuis (dr.J.P Lips) en deels in het VU Medisch Centrum (opleider prof. Dr. H.A.M. Brölmann).

Na het afronden van de opleiding solliciteert ze in de maatschap Gynaecologie van het Maasstad Ziekenhuis, waar ze tot op heden werkt. Haar aandachtgebied is de obstetrie en dan met name maternale ziekten in de zwangerschap. Daarnaast is ze sinds 2012 bestuurslid van het Verloskundig Samenwerkings Verband (VSV) Rotterdam Zuid.

Ze woont in Dordrecht samen met haar echtgenoot Leon Plaisier en hun 2 dochters: Tess (2011) en Emma (2013).

DANKWOORD

Toen dit project begon in 2009 was het de bedoeling een artikel te schrijven over de frequentie en indicaties van zwangerschapsafbreking op maternale indicaties. Het groeide uit tot een promotieonderzoek, waarbij de casuïstiek op landelijk niveau in kaart is gebracht en een bijdrage heeft geleverd aan de nieuwe regelgeving in Nederland omtrent dit onderwerp.

Er zijn flink wat jaren verstreken. Jaren waarin de grootste life-events hebben plaatsgevonden. Jaren waarin successen van geaccepteerde artikelen werden afgewisseld door afwijzingen en soms wanhoop. Jaren waarin ik heb geleerd dat er geen ander vak is op de wereld wat ik zou willen doen.

Dat dit boekje er ligt is aan een heleboel mensen te danken.

Allereerst heel veel dank aan de patiënten die meewerkten aan dit onderzoek. In het bijzonder **Winonah, Hanneke en Amber**. Jullie stemden toe om jullie ervaringen te delen voor in dit proefschrift. Net zoals het op mij diepe indruk heeft gemaakt, weet ik zeker dat dat ook voor de rest van de lezers geldt. Ik ben trots dat jullie verhalen een verdiende plek hebben gekregen.

Mijn promotor, **Prof. Dr. CJM de Groot**, beste Christianne. Ik was nog maar net begonnen met dit project toen jij afdelingshoofd werd in het VU Medisch Centrum. Met je scherpe blik en duidelijke feedback kon ik vaak snel verder als ik even vastgelopen was. Ook het maken van een duidelijke planning heb ik van jou geleerd en heeft me zeker in de laatste fase enorm geholpen. Ik ben er trots op dat het nu af is en ik wil je heel hartelijk danken voor al je adviezen en de fijne samenwerking.

Mijn co-promotores, **Dr. AC Bolte**, lieve Annemieke. Zonder jou was dit proefschrift er niet geweest. Ten eerste natuurlijk omdat dit hele onderzoek door jou bedacht en geïnitieerd is. Ten tweede en wat voor mij nog veel belangrijker is geweest, omdat jij geloofde dat ik het kon. Ik heb mezelf nooit als onderzoeker gezien, maar als clinicus. Het zal voor jou af en toe wel frustrerend geweest zijn, omdat onderzoek doen voor mij compleet nieuw was. Maar je bleef me steunen en stimuleren om het af te maken en daarvoor wil ik je heel hartelijk bedanken. Ik heb enorm veel respect en bewondering voor jouw enorme hoeveelheid kennis en ervaring. Ik vind het fantastisch dat je nu opleider bent in Nijmegen. Heel veel dank voor je steun, de congresbezoeken, de sessies samen als we een artikel bijna af hadden, maar vooral ook voor je luisterend oor als ik die nodig had.

Dr. GG Zeeman, lieve Gerda. Samen met Annemieke stond jij aan de wieg van dit project. Onze eerste ontmoeting kan ik me nog goed herinneren. Ik vond je toen al fantastisch, maar nadat ik de cursus bij je had gedaan hoe om te gaan met incidenten in de patiëntenzorg ben je een voorbeeld voor me geworden en coach op afstand. Want

fouten zijn niet altijd vermijdbaar en als arts draag je die gevolgen vaak lang met je mee. Je enthousiasme heeft me enorm gestimuleerd en ook de bemoedigende woorden aan het begin van elk mailtje waren erg fijn om te lezen, zeker als het even tegenzat. Heel hartelijk bedankt voor de fijne samenwerking.

Leden van de promotie-commissie: **prof. Dr. J.I.P. de Vries, prof. Dr. G. Widdershoven, prof. Dr. A.A.E. Verhagen, prof. Dr. K.W.M. Bloemenkamp, prof.Dr. F. van Bel, dr. R.P. Wijne en dr. IPM. Gaugler-Senden.** Heel hartelijk dank voor het voeren van de oppositie en voor de tijd en energie die het heeft gekost om het proefschrift te lezen en te beoordelen.

Mijn mede-auteurs. **Dr.GCLM Page-Christiaens**, Beste Lieve. Vanuit de grond van mijn hart een heel hartelijk dank je wel voor de fijne samenwerking. Vanaf het begin in 2009 ben jij betrokken geweest bij dit project. Je was altijd de eerste die met de gevraagde revisies kwam en die mij voorzag van een heleboel achtergrond informatie. Je enorme kennis van zaken op het gebied van zwangerschapsafbreking op maternale indicatie heb je altijd gedeeld zodat ik het kon gebruiken bij het schrijven van dit proefschrift. Ik hoop dat je geniet van het leven buiten het ziekenhuis.

Dr. Miriam F van Oostwaard, Prof. Dr, E Pajkrt, Dr JJ Duvekot, Prof. Dr. F Vandenbussche, Prof. Dr. SG Oei, Dr. HCJ Scheepers, Dr. J van Eyck, Dr. JM Middeldorp, Dr. SV Koenen, Ir R de Vries, Dr. I Gaugler-Senden. Bedankt voor al jullie tijd en moeite die jullie hebben gestoken in het meedenken, meeschrijven en reviseren van de verschillende artikelen.

Alle **secretaresses en medewerkers** van de tien centra die hebben geholpen met het verzamelen van alle data. Dank jullie wel!

Mijn paranimfen, Esther Noort-Kuijper en Jolise Martens

Lieve **Esther**. Ik kan me onze eerste kennismaking nog goed herinneren. Ik afdelingsarts op 8B, jij promovendus die patiënten op de afdeling includeerde voor je onderzoek. Ik vond je bos krullen toen al heel tof. Door de jaren heen werd jij mijn steun en toeverlaat tijdens de opleiding, maar ook privé. Trouwen, kindjes krijgen, verhuizen, baan als gynaecoloog. We lopen aardig parallel. Promoveren deed jij 4 jaar geleden (!) als eerste en wat was je goed! Ik bewonder je humor en hoe je alles weet te combineren. We zien elkaar helaas niet vaak genoeg, maar ik verheug me nu al op onze toekomst, inclusief sauna-dates, winkeluitjes etc. Xx

Lieve **Jolise**, mijn fijne rode maat. Toen ik solliciteerde voor een plek in de maatschap vond ik jou de meest kritische. Maar in de positieve zin van het woord. Jij stimuleert mij om mijn ambities waar te maken, om het beste te doen voor de patiënten en om

het beste uit mezelf te halen. Waar jij de tijd vandaan haalt voor al je projecten is voor mij een compleet raadsel. Ik vind je een voorbeeld op de werkvloer, maar bovenal een fantastisch mens. Ik hoop dat we nog heel lang in 1 maatschap zitten. xx

Mijn maatschap, **Jolise, Mustafa, Esther, Petra, Fernando, Hans, Robbert** en chef-de-clinique **Josien**. Wat is het fijn om met jullie in een rode-gele-groene en blauwe maatschap te zitten. Toen ik solliciteerde in 2011 heeft Jolise het voorstel gedaan om tot aan de promotie 1 dag minder te werken. Heel erg bedankt dat dat kon. Jullie wisten toen al dat de combinatie fulltime job, een jong gezin en promoveren geen gelukkige combinatie is, maar dank zij jullie is het gelukt. Ik hoop nog heel veel jaren met jullie te mogen samenwerken.

Een speciaal dankwoord aan **Esther**. Nog niet zo lang geleden was ik door privé gebeurtenissen uit balans en zag niet meer hoe ik alles kon combineren. Ik had het bijna opgegeven en toen was jij daar. Jij maakte mij duidelijk dat ik het mezelf nooit zou vergeven als ik dit niet zou afmaken. Een plan voor overname van diensten was snel door jou gemaakt, ik kreeg weer wat lucht en kon verder. Ik vind het fijn om zo'n maat(je) te hebben. Dank je wel voor je luisterend oor en je steun.

Oud maatschapsleden, **lieve Arie en Henny**. Het is eindelijk af. Ik hoop dat ik zo'n mooie carrière tegemoet ga als jullie hebben gehad. Geniet van de mooie dingen van het leven.

Lieve **Paul***, je zal nooit worden vergeten.

Arts-assistenten, verloskundigen en echoscopisten van het Maasstad Ziekenhuis. Bedankt voor jullie interesse en de gezellige werksfeer. Het is af, volgende week overhoor ik jullie over de inhoud en schrijven we er een protocol over, ok?….geintje.

Dear **Vanessa**, thank you for helping me translate some parts of this thesis. Fortunately you told me my English is "not too bad", thank god… I am happy to work side by side with you. Hopefully for many years more.

(Oud-)opleider, **Dr. JP Lips**, lieve Jos. Bij jou op de afdeling begon in 2002 mijn carrière als dokter en later ook de opleiding tot gynaecoloog. Hoewel ik het misschien niet altijd even duidelijk heb laten merken, ben je een groot voorbeeld voor mij. Je hebt altijd het belang van de opleiding voorop gesteld en mij gestimuleerd het beste uit mezelf te halen. Bij ons laatste gesprek tijdens de opleiding vertelde ik dat ik graag mijn onderzoek wilde bekronen met een proefschrift. Vele jaren later is het af. Bedankt dat je de opleiding zoveel kleur hebt gegeven.

Astrid de Waardt, lieve As, bedankt voor de mooie kaft van dit boek. En bedankt dat jij mijn vriendin bent. Je bezit een groot talent. Tijd om bij elkaar te komen en het te hebben over ons gezamenlijke boek. xx.

Lieve **vrienden en vriendinnen**. Oude en nieuwe vrienden. Vrienden van ver weg en vrienden van dichtbij en letterlijk 1 deur verder. Lachen, uithuilen, genieten van het leven en steunen als het nodig is. Dit project is af. Het is hoog tijd voor het maken van nog meer herinneringen voor later.

Lieve schoonfamilie, **Wim, Jeannette♥, Pascal, Brigitte, Maurice, Inge, François, Ilja en mijn lieve neven en nicht**. Met elkaar en voor elkaar, voor altijd.

Lieve **Rogier, Elwin en Niek, Binck, Thijs en Koen**. De mannen van de familie van Eerden. Wat hebben we veel meegemaakt de afgelopen jaren. Ik hou van jullie.

Lieve zussen, **Marloes en Marjolijn**. Zoals te lezen op de eerste bladzijde van dit boekje is dit proefschrift opgedragen aan jullie. Jullie zijn fantastisch. Lieve Loes en lieve Marjo, ik bewonder jullie moed, doorzettingsvermogen, vechtlust en jullie grote hart voor onze familie. Dat het leven onvoorspelbaar is hebben we in de afgelopen jaren aan den lijve ondervonden. Laten we dicht bij elkaar blijven. Ik hou van jullie, meer dan jullie weten.

Lieve pap en mam. Ik koester onze bijzondere band en ik ben trots dat ik jullie dochter ben. Hard werken heb ik van jullie geleerd. **Pap**, jij bent de rots in de branding. Je bent een fantastische vader, je was vroeger altijd met ons op pad en hielp en ondersteunde waar nodig. Nog steeds geef je mij gevraagd en ongevraagd advies op zoveel gebieden. Je bent absoluut onmisbaar. **Mam**, stoer mens. De laatste jaren zijn niet makkelijk geweest, maar je bent er dankzij je aanpassingsvermogen doorheen gekomen. De band die jij met jouw dochters hebt, wil ik ook met mijn meiden. Ik hou ongelofelijk veel van jullie.

Lieve meiden, **Tess en Emma**. Mijn meiden, mijn mooie meiden. Jullie gekwebbel, gegiebel, jullie levenslust en jullie boze buien. Jullie groeien op tot stoere, zelfverzekerde dames. Ik kan niet wachten om te zien wat het leven nog meer voor jullie in petto heeft. Wat hou ik van jullie. Tot aan de maan en terug.

Lieve **Leon**, I wanna live with you, even when we are ghosts.

Mijn sterke en betere 2e helft. Jouw liefde voor mij en onze dochters maakt me elke dag zo trots. Ik moest naar de andere kant van de wereld om je te vinden, wat ben ik blij dat ik die reis heb gemaakt. Bedankt dat je er bent. Ik hou zoveel van jou. Voor. Altijd. XX